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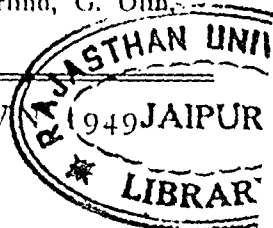
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FACIAL ALLERGIC CANDIDID

By

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(Buenos Aires)

I have named "Facial Allergic Candidid" those allergids localized in the face which have arisen as results of the allergens produced by the fungus *Candida albicans*. The term "Candidid" is new in medical terminology and I was forced to create it in order to identify this type of "id" caused by "Candida albicans". I believe I am the first to describe a facial localization of allergids, specially of the eyelids, produced by the *Candida albicans*, an unpopulated "id". The fungus *Candida albicans* can produce facial and extrafacial candidids, wich may be both populated and unpopulated. I should like to state that it is convenient to accept for the time being, the fact that although most candidids have an allergic pathogenesis, there may also be others that are non-allergic. Unpopulated "ids" are those in which no germs or parasites are present; only the "id" is found, i.d. the result of the action of the distant living agent.

In order to give a name to the allergen that produces the allergic Candidid, I have been compelled to create the word *Candidin*. Candidin is the filtrate resulting from the passage through a Seitz or Berkefeld filter of the glucosa broth in which colonies of *Candida albicans* have grown for 1 or 2 months at room temperature. Only the "S" colonies should be grown in 2 % glucose broth if it is wished to obtain "Candidin" of adeqtuat strength. From the therapeutic viewpoint I believe Candidin should be standardized in units, or direct dilutions such as the house-dust extract.

The etiological factor of Facial Allergic Candidid is the fungus *Candida albicans*. This assertion is supported by the following facts:

(1) The syndrome is produced, worsened and cured by the subcutaneous injection of adequate amounts of Candidin.

(2) All patients possess a focus bearing *Candida albicans*; this focus may be present in the skin, mucous membranes or the intestines.

(3) The speed with which the lesions cure, become worse or are reproduced, cannot be attributed to spontaneous evolution.

(4) Non-specific proteinotherapy cannot be claimed as the reason for the cures.

The pathogenesis of this type of Facial Candidid is *allergy*. The proofs of this statement—which I believe to be the first to be expounded—are the following:

(1) An intradermal injection of Candidin (in an amount sufficient to raise a skin wheal), gives a *late* positive skin reaction identical to the typical infiltration which tuberculin develops in those who are allergic to Koch's bacillus.

(2) There is no mycotic infection in the palpebral locations and in others of the face.

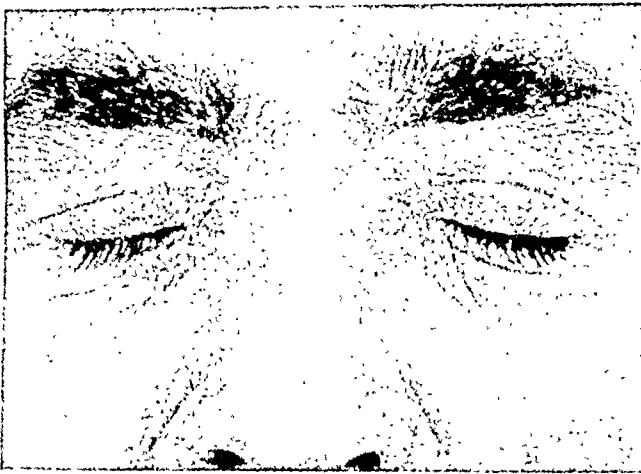
(3) With the administration of Candidin—which contains the specific allergens of *Candida albicans*—the lesions become worse, improve or rapidly cure (depending on the dose injected).

(4) The existence of foci of *Candida albicans* in the skin, mucous membranes or intestines of the patient.

With A. E. Bachmann we failed to carry out passive transmission of antibodies in some patients. As we were unable to find reagins, I believe Facial Allergic Candidid is a type of non-reaginic allergy. However, this does not mean that I deny the possibility of the presence of antibodies. In the meantime this syndrome must be classified as a form of allergy "of infection". Undoubtedly this syndrome is the consequence of a specific alteration acquired and qualitatively dif-

ferent to the reaction capacity of the tissues of individuals bearing one or more parasitic foci of *Candida albicans*.

The Facial Allergic Candidid syndrome is characterized



by the presence of a congestive, dry, scaly and pruritic dermatitis; it appears preferably on the eyelids. It is less frequently found round the mouth and on the chin or neck. The lesions are always bilateral. The eyelid localization is always present and may or may not be accompanied by one or more of the others. Another interesting feature is that the bilateral lesions are always symmetrical. The neck, retro-auricular and peri-

buccal locations are frequently contact dermatitis caused by nail-varnish or streptococcal infection. There are patients who are affected throughout the year by the disease, yet others only show it in Spring and Autumn. Among some of the former the syndrome undergoes seasonal exacerbations. Exacerbations are frequently seen, also, in women just before their periods.

Facial localizations can be accompanied by "populated" or "unpopulated" candidids in the legs or in the forearms and hands.

The palpebral localization—by far the most characteristic—starts by a simple and discreet congestion, which is very pruriginous. The area rapidly becomes scaly though it remains dry. Provided the itching does not give rise to skin erosion, the tegument may appear as an intense furfuraceous desquamation on a brownish background. Of the two sexes, the female is by far the most liable to the disease.

Presumptive diagnosis is based on the aforesaid semeiological characteristics and the face localization, particularly that of the eyelids. The past history, seasonal periodicity and premenstrual exacerbations are also of great assistance. Through an intradermal injection of 1 drop of Candidin (1,000 Coca units per cc.) a positive reaction can be obtained: however, this reaction may be "immediate" or "delayed". The former is of no diagnostic value as it may be due to the peptones contained in the broth in which the *Candida albicans* was grown. We consider the "delayed" reaction as the sole specific one for diagnosis. It usually appears within 24 or more hours of the injection. In some cases there is a late eczematoid reaction on the injection site.

A late skin reaction to Candidin is not indisputable proof of the presence of the Facial Candidid syndrome, yet it can be considered sufficient for diagnosing an allergic condition due to allergens of the *Candida albicans*. The Candidin skin test is frequently positive in people without Facial Candidid. The definite diagnosis is made through the following procedures:

(1) Demonstrating that the lesion is not caused by a mycotic parasitization.

(2) Obtaining evidence that the individual has one or more foci of pathogenous or saprophytic *Candida albicans*.

(3) Observing whether the lesion becomes worse or improves as a result of the skin test with Candidin.

(4) When a rapid cure is achieved by means of "hyper-tolerance" treatment solely with Candidin injections.

Parasitization and allergic reaction may occur at the same time and on the same sites. In these cases the treatment with either ointments or with Candidin may be partially successful, the best being the joint administration of both.

For diagnosis by means of the skin test it is necessary to use an active filtrate, i.e. Candidin obtained from smooth colonies, which have neither aged or become contaminated. It is better to carry out the test with a concentration of 1,000 units total nitrogen per cc., but should this be negative, it ought to be repeated with 10,000 units per cc.

For differential diagnosis in women who use nail-varnish, etc., it is advisable to perform the patch tests.

It is a benign disease which unless complicated by infections either undergoes spontaneous regression or becomes chronic. Because of the pruritus and the facial localization it may affect the nervous system and can give rise to important psychological situations. It may possibly be due to this irritability and nervousness that the syndrome has been classified by skin specialists as a neurodermatitis. I do not deny the great influence of the neuro-vegetative system of the metameric type, which condition is characterised mainly by the bilateralness and symmetry of the lesions.

I have already spoken about the two forms of the Facial Candidid: the permanent and the seasonal. The permanent type is characterized by a tendency to produce a brownish coloration of the skin of the eyelids and keratinization. In all our patients—now more than 30—we have obtained a total cure of what we might call "paroxysm", this means that we have managed to suppress 100 % of the symptoms, treat-

ing intercurrent parasitizations together with any co-existing disfunctions. However, we have been unable to avoid the recurrence of paroxysms, as we lack so far a prophylactic treatment based on Candidin.

The best treatment for Candide is that of specific "hypertolerance" by means of increasing doses of subcutaneous injections of active Candidin of known strength. It is not possible to give a general scheme because the degree of sensitization of each patient should be tested, together with the individual tolerance to the gradient of doses. Among our patients some were cured by 3 Coca units per dose and there was others in which the syndrome was made worse with 4 units. In other instances a cure was not achieved until 1000 units per dose had been injected. The interval between therapeutic doses may vary.

Treatment must be adapted to every patient, regulating in each the starting dose, the intervals, the increases, the useful dose and that of maintenance. Tolerance should be assessed by means of the local and focal reactions.

We have not had a single accident of the "anaphylactic shock" type after several thousands of injections of Candidin, in some cases using doses as high as 7,000 Coca units. The only mishap we have seen—a disagreeable one, but not dangerous—is the worsening of the syndrome; on the other hand, when this occurs, it serves to confirm the diagnosis and help us to foretell that treatment will be successful as soon as the dose is adjusted.

The treatment based on Candidin is by far the best and may be the only one, but not always. Any organic disfunctions, foci of infection parasitizations etc., should also be treated.

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HEPARIN HYPERSENSITIVITY

By

I. C. HØJENSGÅRD and MICHAEL SCHWARTZ

When using heparin for the treatment of thrombosis it is generally supposed that heparin has got no other effects than the prevention of coagulation, *i.e.* that it especially has no secondary effects on the human organism.

During the first years that heparin was used it was found, however, that in some cases the substance had a *toxic effect* (Reed and Lamson 1926, Kirkegaard 1942, Wulff 1942, Crafoord and Jorpes (1942)), but it can be taken for granted that these reactions (chills, pyrexia, headache, lumbar pains etc., appearing 1-2 hours after the injection of heparin) were caused by impurities in the heparin preparations (Reed and Lamson 1926, Astrup 1944). Since a better purified product has been produced no such cases have been recorded, and commercial heparin is now regarded as being completely free from toxic effects.

Furthermore a few cases of *allergic reactions* after the administration of heparin are mentioned in medical literature. It concerns some cases recorded from Sweden (Jorpes 1941, Crafoord and Jorpes 1942, Hellsten 1942, Zilliacus 1946, Jorpes 1946), and a single case from U.S.A. (Grolnick and Loewe 1947). — The Swedish cases, apparently only four in all, have not been described in detail, but are only mentioned as "true anaphylactic reactions", and they are said all

to have taken place before 1942, and therefore there has been a tendency to regard them as caused by impurities, which are not found in the more purified heparin preparations of later years.—In *Grolnick* and *Loewe*'s case the reaction appeared as widespread erythema, chills and fever, and the patient developed urticaria during desensitization. Intracutaneous reactions with heparin were positive and Prausnitz-Küstner's reaction proved positive. Skin reactions with "beef-extracts" and beef-liver-extracts were negative at the first examination. Several months later—after successful desensitization with heparin—a repeated test showed positive skin reaction, not only with heparin but also with beef-serum and with extracts from ox-lungs, and the Prausnitz-Küstner reaction was now positive with all these substances.

Apparently all the cases mentioned have appeared after prolonged treatment with heparin or in relation to the renewal of heparin treatment, and it would therefore appear that they have been cases of active sensitization either with heparin or with possible impurities, or probably with both.

In certain antigen-antibody reactions, especially in the case of anaphylactic shock, a prolongation of the clotting time of the blood is noted, and the cause for this is supposed to be a (secondary) release of heparin. The latter is not supposed to have any influence on the antigen-antibody reaction as such, however. As the clinical signs and symptoms of the antigen-antibody reaction cannot be completely explained as a histamine effect, as is shown by the prolongation of the clotting time of the blood, it would appear that there is a heparin-like component in the pathogenesis of anaphylactic shock. Whether heparin itself can have an antigen effect is uncertain. In animal tests *Reed* and *Lamson* (1926) and *Reynert* and *Winterstein* (1939) have found that "pure" heparin is completely lacking in antigen power.

However, it is not yet possible to produce chemically pure heparin. The commercial preparation is stated to be a solution of crystalline heparin, but the crystalline character is doubtful and the substance presumably is not homogeneous. In any

case it is not possible to produce different preparations with identical biological activity even from the same original material. It is also possible that, chemically, heparin is different in various animal species. (*Astrup* 1944, *Jorpes* 1946).

Although it should be possible to produce heparin in a pure crystalline and apparently completely identical state from different animal sources it would hardly exclude in advance the possibility of the potency of the substance to produce allergic reactions. Cases of insulin allergy are known, e.g., in man, where the apparently completely pure, often recrystallized insulin still provokes the same allergic reactions, independently of the kind of animal pancreas used for the preparation.

The literature referred to is, as mentioned above, concerning sensitization developed during heparin treatment. What might be called *spontaneous heparin allergy* does not seem to have been recorded. At the Surgical Clinic C of Rigshospitalet we are of opinion that we have observed such a case.

CASE REPORT

RH, C-1262/47. A 51 year old man. In-patient from June 2nd to July 8th 1947.

As a child the patient had pleurisy, allegedly followed by a heart affection which, however, has never worried him. As an adult he has had attacks of palpitation which, following a doctor's examination, was described as paroxysmatic tachycardia. There have never been symptoms of decompensation. The patient has been a keen mountaineer.

He was admitted to this hospital for bilateral inguinal hernia of recent origin, following hard forestry-work to which he was unused. On June 3rd a radical Bassini operation was performed on both sides. The next day he was out of bed. From June 5th to June 9th the temperature was raised (max. 39.3), and for this reason the patient was made to remain in bed. A basal dullness on both sides with slight crepitation was found on examination of the chest. Penicillin (100,000 units 3 times daily) and sulphathiazole (1 g 3 times daily) was given. On June 9th the temperature was normal, the patient felt well and was allowed out of bed.

On June 12th and 13th again a slight increase in temperature was noted, and the patient was complaining of "stinging" pains in the right side of the chest and also of meteorism and inability to pass flatus. Further examination

of the chest showed marked dullness on the right side at the back. Those symptoms diminished slowly in the following days during renewed penicillin and sulphathiazole therapy, as previously.

June 23rd: During the last two days the patient has suffered several times from suddenly occurring attacks of pain in the chest, accentuated by respiration and accompanied by anxiety and dyspnoea, blanching and cold sweat. The pulse was not very much affected. No expectoration.—These attacks were said to be quite different from the patient's earlier paroxysms of tachycardia. Again meteorism and inability to pass flatus was complained of. The extremities were normal. Stethoscopic examination of the lungs showed a definite basal dullness on the right side, and following pleural puncture 300 cc. of sero-hemorrhagic fluid was obtained.

It was now thought to be a case of thrombosis of the pelvic veins with recurring pulmonary emboli. Heparin treatment was instituted, and for the first injection heparin LEO 5 % 3 cc. (= 150 mg.) was given intravenously. Immediately after the injection had been given the patient had flushing of the skin especially marked in the face, and complained of a strong feeling of distress. The pulse was accelerated but of good volume, and the action of the heart was regular. The blood pressure was not taken. The attack passed off in the course of a few minutes. After that numerous urticarial elements measuring up to 2 cm were found all over the skin with the exception of the face. These disappeared after a few hours leaving no after-effects. No oedema was found.

The treatment was changed to Synparin (dicoumarol), and the pulmonary symptoms disappeared in a few days. On July 3rd stethoscopic examination of the lungs proved normal and on July 8th the patient was discharged feeling well.

The attack described above gave a suspicion that the patient had a heparin hypersensitivity, which we tried to verify: about one hour after the alleged shock we performed intracutaneous tests with (1) undiluted heparin from the ampoule from which the injected heparin had been taken, (2) heparin from another ampoule of heparin LEO, and (3) heparin VITRUM (Swedish preparation). All three heparin preparations gave similar strong positive urticarial skin reactions (+++ reaction with clearly defined pseudopodia). With control tests on several normal persons with the above-named heparin preparations negative reactions were found.—3 hours after the shock blood was taken from the patient in order to examine it for circulating antibodies. In this test we were unable to prove conclusively the allergic etiology of the shock,

as Prausnitz-Küstner's reaction was negative. The patient stated that he had never previously had heparin or serum and likewise no previous allergic diseases.

It must therefore be concluded from the above that the patient has had an acute general allergic reaction as a result of heparin allergy. The LEO medical laboratories state that heparin is prepared from ox-lungs. Unfortunately we were unable to examine the patient for beef-allergy, as immediately after his discharge from the hospital he went abroad. As stated above a positive result of the Prausnitz-Küstner reaction would have proved the diagnosis, but a negative result cannot disprove it, as the reaction only gives evidence of circulating antibodies, and these might have been used up during the shock.

DISCUSSION

Neither this case nor those mentioned in the literature can answer the question as to whether a "pure heparin allergy" exists, or whether the recorded allergic reactions are caused either by impurities or by heparin varying in different animal species. In *Grolnick* and *Loewe's* case an allergy for ox-serum and beef-lung-extract was found after the patient received a prolonged heparin treatment. The accurate connection between beef- and heparin-allergy cannot be made clear with any certainty in the case of these authors; probably both forms of allergy are due to the heparin treatment, but one cannot completely discount the possibility that the beef-allergy was brought on by the intracutaneous tests with "beef-extracts" and beef-liver-extract which were previously given.

On the contrary these cases show that with the heparin preparations available for therapy to-day one must be aware of the possibility of a sensitization, and that in certain still rarer instances one can meet cases of apparently "spontaneous heparin allergy". It must therefore be considered necessary in treatment with heparin to have available means of combating shock, such as adrenalin. *Jorpes* (1946) proposes

that taking into account the possibility of allergic shock, heparin treatment should always be preceded by a test dose of 25 mg. One can perhaps discuss the advisability of giving so large a dose in testing for hypersensitivity; in any case intravenous injection as a test for hypersensitivity would appear to entail considerable risk.

If it is necessary in a case of heparin allergy to carry out anticoagulation treatment, desensitization may be tried or the treatment may be continued with dicoumarol.

SUMMARY

A case of apparently spontaneous heparin allergy is recorded, characterized by mild shock, general erythema and urticaria. Intracutaneous reactions gave positive results with heparin of different makes, but Prausnitz-Küstner's test was negative. The therapeutic consequences are sketched, and the necessity of having adrenalin available when giving heparin is pointed out.

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ADDED BY THE PROOF-READING

It would appear that "spontaneous heparin allergy" perhaps is not so rare as we thought it to be. According to *deTakáts* (Journal internat. de chir. 8: 903, 1948) a sur-

prising number of individuals show increased reactivity to heparin even though they never had heparin before. This reaction is described by *deTakáts* just as in our case report.— In his brief report *deTakáts* unfortunately does not mention any case histories, clinical allergy tests, or references as support to his statement.

A STUDY ON THE EFFECT OF ULTRAVIOLET LIGHT ON ALLERGIC IMMEDIATE WHEEL SKIN REACTIONS

By

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One of the most important and most pronounced features in the Besnier's prurigo symptomatology is the decrease of the illness or often a complete disappearance of it in summertime. The cause is unknown. It may be easily imagined that the improvement is a consequence of the increased radiation of sunlight on the skin. This is also often the patients' idea based upon their own personal impressions. Thus the patients do not seldom state that the more they sunbathe the more quickly and effectively does the skin heal.

The sunlight may in several ways have this effect e.g. because of increased formation and accumulation of D-vitamins, increased blood circulation in the thickened, infiltrated skin with an improved resorbent ability. As the disease is considered to be an allergic complaint the improvement can, however, also be thought to depend upon an obstruction of the allergic reactions through the direct influence of sunlight.

In order to continue the discussion it is important to be reminded of the fact that the formation of immediate wheals in the skin are influenced by the edematous condition of it. In works by *Pilcher* and *Sollmann* (1924) and by *Pilcher* (1926) it is emphasised that the formation of a wheal after an injection of e.g. histamine depends upon the blood circulation in the part of the body in question and that the wheal becomes smaller, when the skin is edematous whatever the cause of this may be. If the skin is radiated with ultraviolet rays from e.g. a mercury vapour lamp an erythema arises, that is an inflammatory edema, in which

only a small or possibly no wheal at all appears when injecting histmine (*Lewis* 1927).

It has nevertheless been ascertained by *Albus* and *Feldermann* in 1938 that the radiation of ultraviolet rays on one part of the skin brings about an abated influence in allergic immediate wheal skin reactions also on such parts of the skin as have not been radiated, so-called "far distance" effect. The two scientists have come to this result in the following way: *Albus* considered that he in 1937, had proved in an investigation that if one gave a person with 3 to 4 days' interval an allergen injection which he or she was hypersensitive to, an intensification was caused in the hypersensitivity expressing in volume increased immediate wheal reactions. Taking this result into consideration *Albus* and *Feldermann* show how sensibility acted when the radiation of ultraviolet rays is performed on the skin. The two authors tested 32 persons suffering from allergic diseases of different kinds. On 14 of these the testing was repeated after 2 more days. The increase of the size of the wheals after the first examination was recorded. It averaged 135 %. The other 18 patients were radiated after the testing with mercury vapour light "Original Hanau", for 5 minutes. 10 of these cases were radiated on the front of their bodies, 8 on their backs where the testing had been performed. *Albus* and *Feldermann* found in this way at the testing after still another day in the first group wheals which were 72 % smaller, and in the second group wheals which were 86 % smaller than at the first examination. Added to the recorded decrease is, according to the opinion of the authors, the increase that would have appeared simultaneously as a consequence of the first allergen supply, provided mercury vapour light radiation had not been given. In conformity to the calculations by the authors the real decrease was when the front part of the body was radiated 207 % and when the back was thus treated 221 %. In the first case it would thus be a matter of but a "far distance" effect, that *Albus* and *Feldermann* consider depending on the formation of "thiol"-substances when radiating with ultraviolet light.

With regard to what has been stated in the introduction and the difficulties we have to master the allergic diseases, the tests

related in connection with mercury vapour light are of very great interest. By using mercury vapour lamps therapeutically in the correct way one ought to have, it seems, an effective means against various allergic diseases. Thus it has interested me to study the effect of the mercury vapour light on allergic wheal reactions with a mode of procedure in which one may straightaway record the abating influence without needing to calculate with a stimulating factor at the same time.

The writer's investigations. Method used: The author has in his investigations passively sensibilized (in accordance with the Praunitz-Küstner's method) a number of persons, principally men, in most cases free from dermatoses and allergic diseases. In a few cases patients suffering from Besnier's prurigo have been tested. By control testings the author has assured himself of the fact that the experimental persons have not to begin with been allergic against the allergen used. On those persons passive sensibilization has on two or three occasions been performed with a couple of days' interval in one place on each side of the back simultaneously. After the first couple of Prausnitz-Küstner's experiments (Pr.-K.) having been performed, the patients were radiated with mercury vapour light. This radiation has in certain cases been done on the right side of the back where passive transference has taken place, in other cases on the abdomen. By comparing the sizes of the reactions on both sides of the back obtained after the radiation with the corresponding results of the two first Prausnitz-Küstner's tests we get a possibility to note the effect direct or indirect of the mercury vapour light on the antigen-antibody reactions. There is no reason to suppose that the reactions first performed have actually influenced those following, as each such reaction is an isolated phenomenon. In a number of control cases which have not been radiated at the same time with mercury vapour light the correctness of this view has been confirmed.

Antibody-serum has been obtained from patients hypersensitive to horse danders and dandelion allergens. Blood from these has been forwarded to the State Bacteriological Laboratory where a serum has been obtained that has been put into ampoules of 1-2 mil. Control of sterility has been done and the ampoules

have been kept in a refrigerator. In this way the author has always been able to inject a serum with the same percentage of antibodies at each Prausnitz-Küstner's test on the same person. It is important to take care that the serum used is not affected by an allergen which is daily brought into the organism e.g. food-allergen or dust. As is already mentioned horse danders or dandelion pollen allergen have been used instead, while the testing has taken place in winter and on persons having had no contact with hay or horses or have not been lying on horsehair mattresses.

The passive sensibilizing, as has been previously mentioned, has been performed in 2 or 3 seances with an injection of 0.1 mil. serum simultaneously on each side of the back. For the injection of serum the same syringe has always been used on the same person. The spots for the injections have been chosen about 4 to 5 centimetres from the previous injections on the same side and in the same horizontal plane as these above or just below the spinae scapulae. Within these areas of the back one gets the most regular reactions. The first injections have been done medially, with those following laterally from the first ones or, vice versa, the first ones laterally and the others medially. The centre of the serum wheals has been marked in order to facilitate an exact injection of allergen 48 hours later. On each experimental person 0.05 mil. allergen of the same strength and with the same syringe has always been injected. On the other hand the strength of the allergen has changed somewhat from one case to another.

All these tests have been performed in the evenings. 48 hours after the serum injections the allergen has been injected. The two injections of the allergin have followed one another in the most rapid tempo so as to avoid any "far distance" effect from either side respectively. It is important that the patients during the tests have always been sitting in the same way, slightly bent forward with the lower arms resting on their knees. The antigen-antibody reactions received have been registered exactly 15 minutes after the allergen injections. The periphery of the wheals has been outlined in ink and copied on to a piece of transparent paper. The area has then been measured in square-centimetres with a

planimeter with which several measurements have always been taken.

The radiation of light has been performed with a mercury vapour lamp of "Original Hanau" type. Some patients have been radiated on the abdomen or the whole of the front, others on the whole right side of the back or on the upper part of the right side of the back within a limited part where the sensibilizing tests are to be done. The other side of the back has then been covered with lead-slabs so as to guard this part completely from the light. In all the cases the radiation has been accommodated according

TABLE 1

Pat.	Pr.-K.	Left	Right	Pat.	Pr.-K.	Left	Right
1. I. T.	1. 26/2	2.17	2.20	5. B. H.	1. 27/10	1.26	1.26
	2. 29/2	2.20	—		2. 31/10	1.50	1.55
	3. 3/3	2.40	2.03		3. 3/11	1.30	1.40
2. G. K.	1. 26/2	1.55	1.55	6. M. K.	1. 27/10	1.92	1.54
	2. 29/2	—	1.70		2. 31/10	1.60	1.48
	3. 3/3	1.98	2.00		3. 3/11	1.70	1.67
3. N. R.	1. 26/2	1.50	1.43	7. N. K.	1. 26/2	1.00	1.00
	2. 29/2	—	1.96		2. 3/3	0.75	—
	3. 3/3	—	1.57		3. 6/3	0.76	0.90
4. N. F.	1. 5/11	2.50	2.26	8. B. Fr.	1. 5/11	1.90	2.15
	2. 9/11	2.18	2.10		2. 9/11	1.70	1.88
	3. 12/11	2.26	2.35		3. 12/11	2.00	2.00

In the above table 1 investigations with passive sensibilizing (Pr.-K.) are demonstrated partly on the left, partly on the right side of the back upon 8 non-allergic persons. On each one this has been done on 3 occasions at times given in the table. In cases 1-4 the first serum injections took place bilaterally medially on the back and the following ones laterally from there, all in the same horizontal plane. In cases 5-8 the first injections have been done laterally and the following ones medially from there. Simultaneous radiation has not been undertaken in this group.

It appears from the table 1 that on each of the persons as a rule were rather small differences between the sizes of the reactions in the various investigations. These differences do not indicate any natural tendency in the Prausnitz-Küstner's test to increase or to decrease in repeated tests on the same non-allergic person.

TABLE 2

Pât.	Pr.-K.	Left	Right	Remarks	
1. A. K.	1. 27/11	1.60	1.82		
	2. 1/12	1.70	1.60	1/12	Slight erythema.
2. K. B.	1. 22/11	1.76	1.82		
	2. 26/11	2.12	2.05	26/11	Pronounced erythema.
	3. 29/11	2.05	2.80	29/11	Pronounced erythema.
3. B. L.	1. 22/11	1.70	1.64		
	2. 26/11	1.50	1.88	26/11	Medium erythema.
	3. 29/11	1.70	1.73	29/11	Pronounced erythema.
4. K. K.	1. 24/3	2.06	1.76		
	2. 27/3	2.00	1.86	27/3	No erythema.
	3. 1/4	2.06	1.96	1/4	Pronounced erythema.
5. E. L.	1. 18/2	—	2.66		
	2. 21/2	—	2.70	21/2	No erythema.
	3. 25/2	—	3.06	25/2	Pronounced erythema.
6. V. N.	1. 24/3	1.85	1.97		
	2. 27/3	2.07	2.30	27/3	Slight erythema.
	3. 1/4	1.90	1.96	1/4	Pronounced erythema.
7. Fr. V.	1. 24/3	1.20	1.33		
	2. 27/3	1.02	1.37	27/3	No erythema.
	3. 1/4	1.03	1.03	1/4	Pronounced erythema.
8. O. H.	1. 24/3	1.16	1.40		
	2. 27/3	1.37	1.40	27/3	No erythema.
	3. 1/4	1.02	1.24	1/4	Pronounced erythema.

The table 2 gives an account of 8 non-allergic persons who have been passively sensibilized and who have also been radiated with mercury vapour light on the whole abdomen several days in succession. The first 3 cases have been radiated in small doses also on the whole front part of the body.

By comparing the tables 1 and 2 we find similar variations in the sizes of the repeated Prausnitz-Küstner's reactions on non-allergic persons when the abdomen was or was not radiated with mercury vapour light in varying doses.

to the individual reaction after the first test dose of, as a rule, 3-4 minutes' radiation with the lamp at about 60 centimetres' distance. In some cases the radiation has been arranged so that only a slight erythema has been indicated on a large area. In

TABLE 3

Pat.	Pr.-K.	Left	Right	Remarks	
1. G. T.	1. 11/11	1.30	1.38		
	2. 15/11	1.47	1.50	15/11	No erythema.
	3. 18/11	1.46	1.53	18/11	No erythema.
2. B. K.	1. 11/11	2.84	3.00		
	2. 15/11	2.45	2.86	15/11	Slight erythema.
	3. 18/11	3.60	3.10	18/11	No erythema.
3. M. H.	1. 11/11	2.70	2.05		
	2. 15/11	2.06	2.10	15/11	Slight erythema.
	3. 18/11	2.15	1.95	18/11	No erythema.
4. M. J.	1. 11/2	1.85	2.20		
	2. 14/2	2.33	2.25	14/2	Slight erythema.
5. T. H.	1. 18/2	1.50	1.46		
	2. 21/2	1.32	1.40	21/2	Slight erythema.
6. H. V.	1. 22/11	1.90	2.00		
	2. 26/11	1.87	1.75	26/11	Medium erythema.
	3. 29/11	2.70	2.54	29/11	Erythema fading.

The table 3 gives an account of 6 non-allergic persons radiated several days in succession with mercury vapour light over the whole right side of the back. The radiation has been adjusted so that only slight erythema has arisen.

In the table 3 the repeated Prausnitz-Küstner's reactions on both sides of the back show the similar size variations as in the tables 1 and 2.

other cases, radiation has on the other hand been given more forcibly over a smaller area, especially where serum injections are to be performed. As a rule patients have been radiated several days in succession after the first Prausnitz-Küstner's tests have been done. In one or two cases Prausnitz-Küstner's tests have been performed within the part of the skin where a marked erythema has already become extinct. So as to remove or at least to decrease a possible simultaneous sunlight effect, the investigation has been done wholly during the winter months and on such persons as have had indoor-work.

The *results* of the Prausnitz-Küstner's tests are demonstrated in the tables 1-5. The dates indicated mark when the allergens

TABLE 4

Pat.	Pr.-K.	Left	Right		Remarks
1. G. Ö.	1. 27/10	2.22	2.32		
	2. 31/10	2.20	2.35	31/10	No erythema.
	3. 3/11	3.15	1.83	3/11	Pronounced erythema.
2. H. K.	1. 11/2	2.88	3.15		
	2. 14/2	2.56	3.32	14/2	Slight erythema.
	3. 17/2	2.92	2.50	17/2	Pronounced erythema.
3. G. Bl.	1. 18/2	2.27	2.30		
	2. 21/2	2.24	2.50	21/2	No erythema.
	3. 25/2	2.76	2.00	25/2	Pronounced erythema.
4. G. F.	1. 27/10	1.94	2.52		
	2. 31/10	1.58	1.60	31/10	No erythema.
	3. 3/11	1.40	1.27	3/11	Pronounced erythema.
5. V. Ö.	1. 5/11	3.08	3.12		
	2. 9/11	2.40	2.60	9/11	Pronounced erythema.
	3. 12/11	2.38	1.80	12/11	Pronounced erythema.
6. N. St.	1. 29/3	2.25	2.26		
	2. 4/4	2.13	1.53	4/4	Pronounced erythema.
7. A. Ö.	1. 29/3	2.06	2.10		
	2. 4/4	1.56	1.10	4/4	Pronounced erythema.
8. K. V.	1. 11/2	1.95	1.83		
	2. 14/2	2.05	2.13	14/2	Slight erythema.
	3. 17/2	1.65	1.55	17/2	Pronounced erythema.
9. N. K.	1. 27/4	1.60	1.60	5/5	A pronounced erythema
	2. 5/5	1.20	1.86		extinct on 1/5.
10. J. V.	1. 27/4	1.93	1.83	5/5	A pronounced erythema
	2. 5/5	2.56	2.47		extinct on 3/5.

The table 4 demonstrates 10 non-allergic persons who have been radiated with mercury vapour light several days in succession within a small area on the upper part of the right side of the back, where the passive transfer has been performed. The cases 1-4 have apart from effective radiation on the small area on the upper part of the back, also been given mercury vapour light in small doses on the whole of the right side of the back. In cases 9 and 10 passive transfer within an area where a pronounced erythema has become extinct 3 to 4 days before the Prausnitz-Küstner's tests.

In all cases 1-8 where the Prausnitz-Küstner's tests have been performed on the right side of the back in a skin with a pronounced erythema we find distinctly smaller reactions after the radiation. On the contrary in cases 9-10

TABLE 5

Pat.	Pr.-K.	Left	Right	Remarks	
1. R.	1. 26/1	1.55	1.62		
	2. 29/1	1.40	1.20	29/1	Slight erythema.
2. K.	1. 24/11	1.12	0.96		
	2. 28/11	1.10	1.07	28/11	Slight erythema.
	3. 1/12	0.96	1.05	1/12	Slight erythema.
3. W.	1. 24/11	1.00	0.96		
	2. 29/11	1.06	0.92	29/11	Slight erythema.
	3. 2/12	0.95	1.05	2/12	Slight erythema.
4. T. D.	1. 28/11	1.35	1.42		
	2. 2/12	1.16	1.06	2/12	Pronounced erythema.
	3. 6/12	1.23	1.02	6/12	Pronounced erythema.
5. S. K.	1. 26/1	0.96	0.90		
	2. 28/1	0.94	1.11	28/1	No erythema.
	3. 1/2	1.00	0.75	1/2	Pronounced erythema.
6. A. Th.	1. 28/11	2.52	2.60		
	2. 2/12	2.92	2.60	2/12	Medium erythema.
	3. 6/12	2.12	1.80	6/12	Pronounced erythema.
7. Sv. H.	1. 15/11	1.05	1.03		
	2. 19/11	0.90	0.55	19/11	Pronounced erythema.
8. Fr. L.	1. 6/12	1.86	1.83		
	2. 10/12	1.46	1.20	10/12	No erythema.
	3. 14/12	1.55	1.30	14/12	Pronounced erythema.
9. G. S.	1. 15/11	1.60	1.70		
	2. 19/11	1.95	1.25	19/11	Pronounced erythema.
	3. 22/11	1.74	1.25	22/11	Pronounced erythema.
10. U. D.	1. 7/2	1.80	1.95		
	2. 9/2	1.90	1.76	9/2	Slight erythema.
	3. 12/2	1.63	1.26	12/2	Pronounced erythema.
11. J. J.	1. 1/2	1.56	1.70		
	2. 4/2	2.10	1.85	4/2	Slight erythema.
	3. 7/2	2.00	1.36	7/2	Pronounced erythema.

on which the investigations have been performed in a skin where a pronounced erythema has just become extinct, the reactions were larger than before the radiation. By comparing the reactions obtained on the left side with the corresponding reactions in the table 1 we find no definite dissimilarity in the manner of reaction. 3 of the 4 most forcibly radiated persons have shown increased reactions after the radiation.

In the table 5 there is an account of 11 cases of Besnier's prurigo, these patients have been passively sensibilized and simultaneously radiated with mercury vapour light for several days in succession. Case 1 has been radiated on the abdomen. Cases 2-3 have been radiated on the whole of the right side with rather weak doses. The others have been radiated with large doses within a small area on the upper part of the right side of the back where the passive sensibilizing has been done.

All the most forcibly radiated cases 4-11 showed in the tests on the right side in a skin with pronounced erythema smaller reactions than before the radiation. On the left side both larger and smaller reactions were obtained. Several persons have shown such small variations in the sizes of the reactions in the repeated tests that in the results we cannot find any definite indirect influence ("for distance" effect) of the mercury vapour light on the allergic wheal reactions.

have been injected at the same time on the right and the left sides of the back. The sizes of the reactions have always been given in square-centimetres. In the tables 2-5 the intensity of the erythema when carrying out the above tests is shown under "Remarks". In rare cases e.g. 1-3 in the table 1 some technical mishaps have prevented performing the investigations constantly on both sides of the back.

The results of the investigation may be summarized in the following *conclusions*.

1. It may be expected that if the Prausnitz-Küstner's tests on the same person are executed over and over again with some day's interval, under the self-same outward circumstances, previously drawn up, then the latter reactions are not influenced by the first ones in any noticeable degree. The results in table 1, but also those of the other tables confirm the justice of this conception. The wheals obtained are reciprocally so much of the same size that with this method one ought to be able to study the influence of an outward momentum on the allergic immediate wheal reactions. The results in tables 4 and 5 confirm this.
2. The tests with mercury vapour light have not definitely been able to reveal any indirect abating effect ("far distance" effect) on the allergic skin reactions after a few days' radiation.
3. On the other hand these reactions become less pronounced

if the tests are performed in erythematous skin after the radiation of mercury vapour light, when this is sufficiently powerful. The unitary results in the tables 4 and 5 warrant this. When carrying out the tests this has been actually still more noticeable than what the figures show, as it is then possible to note that the wheals in the erythematous skin have become lower and more flaccid. The diminution pointed out is in complete agreement with the observations by *Lewis* and this is probably the issue of the inflammatory edema. In favour of this speaks, among other things, for the fact that in the two cases that had been tested immediately after the erythema was extinct, the wheals had developed normally.

4. In patients with or without allergic diseases, the results have remained similar in these matters.
5. Even if the allergic immediate wheal skin reactions appear smaller in an erythematous skin as the consequence of the radiation of mercury vapour light the author, however, dare not from this conclude that the sunlight causes by such a reaction abating influence any decrease of the symptoms of Besnier's prurigo during the summer months.

S U M M A R Y

The author has in his investigations tried to show a possible influence of the mercury vapour light on the allergic cutaneous immediate wheal reactions. Prausnitz-Küstner's test has been performed at the same time on the right and left sides of the back on two or three occasions after one another on the same person. With the exception of 8 all of the 43 experimental persons have after the first couple of Prausnitz-Küstner's tests been radiated with mercury vapour light in varying doses on the abdomen or on the right side of the back where the test has been performed. By comparing the sizes of the reactions on both sides of the back obtained after the radiation with corresponding results of the first two Prausnitz-Küstner's tests we get a possibility to note the effect direct or indirect of the mercury vapour light on the antigen-antibody reactions.

The author found that in the repeated Prausnitz-Küstner's tests on the same person with the given experimental conditions we got rather small variations in the sizes of the different reactions. Any natural tendency in these to increase or to decrease was not noticed. The tests performed in a pronounced erythematous skin showed distinctly smaller reactions than before the radiation. In a weakly radiated skin with slight or no erythema there did not appear any definite influence on the sizes of the reactions.

Any definite influence on the sizes of the reactions in a non-radiated skin caused by the weak or forcible radiation of another skin area could not be shown. It seems as if allergic persons reacted as non-allergic persons in above-mentioned respects.

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SOME VASCULAR EFFECTS OF N-DIMETHYLAMINO-METHYLETHYL-DIBENZO- PARATHIAZINE (PHENERGAN)

By

SIGMUND GLANZMANN and J. ANTONIO SALVÀ MIQUEL

The subject of this study is the compound 3277 R.P., the most active of the phenothiazinic series introduced by Halpern & Ducrot¹, as regards

- (a) its immediate effects on arterial pressure,
- (b) its influence on the hypotensory response to acetylcholine of blood pressure and
- (c) its influence on the hypertensory response to adrenaline of blood pressure.

This work was started by one of us in the course of a comparative study on a number of antihistaminic substances.²

METHODS

The experiments of groups (a) and (b) were performed on cats weighing from 2 to 3 kgs. which were anesthetized with 50 mgs/kg of dial given intraperitoneally one hour before the start of the experiment. Some of these animals had their vagus nerves cut.

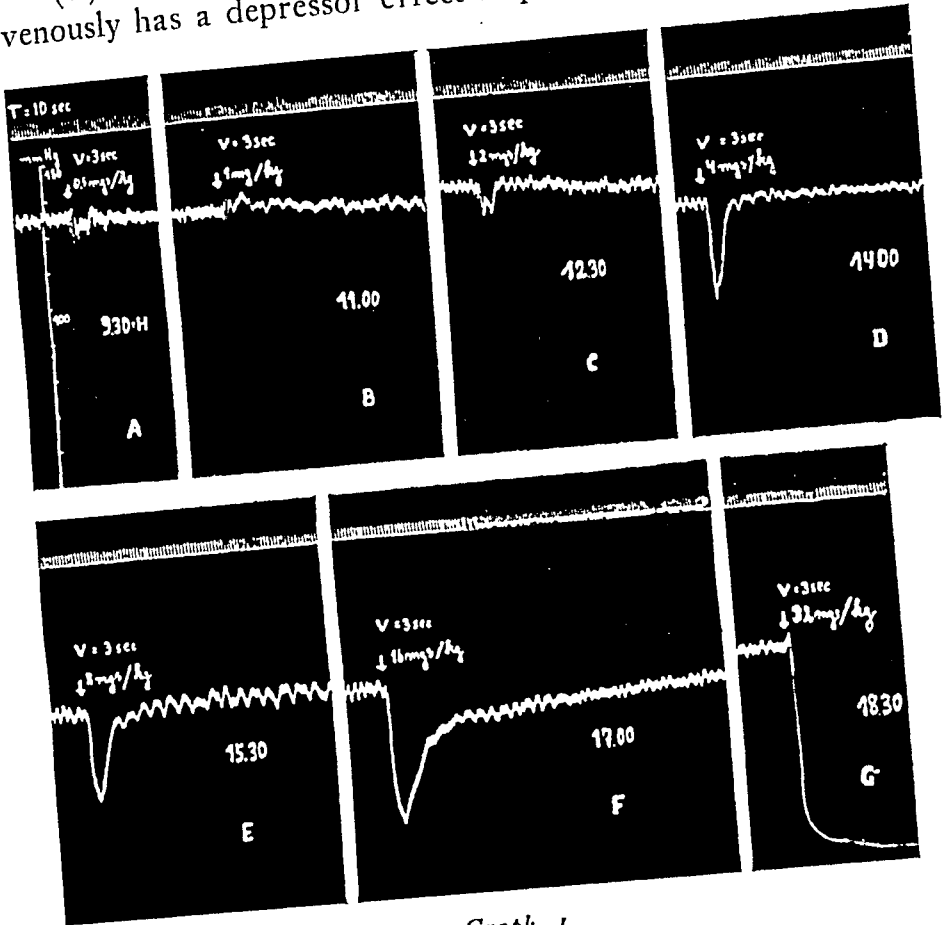
The experiments of group (c) were studied on the spinal cat prepared according to Elliot's method.

In all cases, i.e. 18 cats, the blood pressure was registered on a smoked cylinder by means of a mercury manometer connected with a carotid artery. All the substances mentioned

above were injected intravenously into a femoral vein cleared for the purpose.

RESULTS

(a) *Effects on arterial pressure*: Phenergan given intravenously has a depressor effect in proportion to the amount

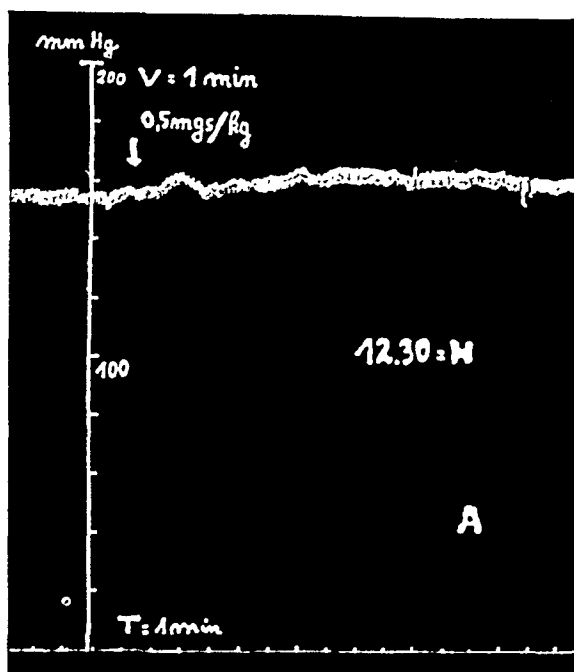


Graph. 1.

Cat of 2,500 kgs. Effect of increasing doses of Phenergan, given intravenously on the A. P. Volume of injection for all doses was constant (1 c.c.). T: time. V: duration of injection. H: hour.

injected (see Graph. 1). With a dosage smaller than 1 mg/kg there is generally a diphasic phenomenon of hypotension followed by a temporary rise in pressure. This last phase may be the only one with these smaller doses (see Graph. 1 B and 2).

The extent to which pressure is lowered and also the time and manner of recovery for the same dose is of course related to the speed of injection of the antihistaminic compound. Graph. 3 shows the above-mentioned variations observed on a cat which had the same dose injected several times at equal intervals but with varying injection speed.



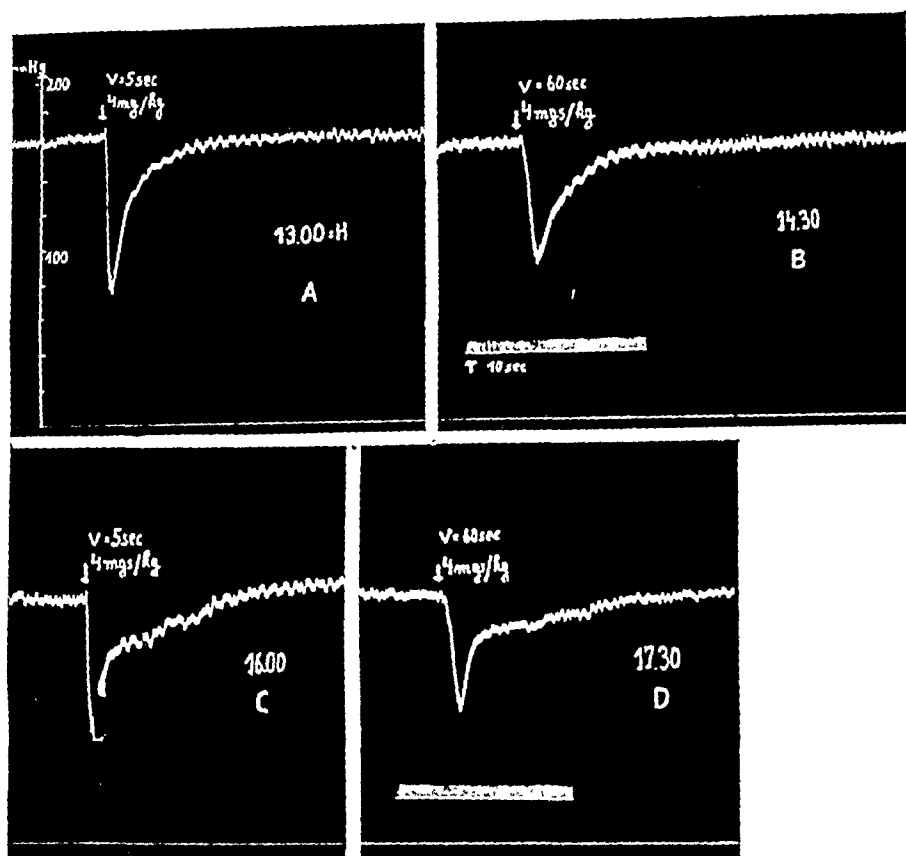
Graph. 2.

Cat of 2.800 kgs. Effect of 0.5 mgs/kg intravenous Phenergan on the A. P.
V duration of injection: H: hour. T: time.

(b) *Effects on the vascular response to acetylcholine:* Phenergan does not alter the depressor effect of acetylcholine. Different doses of Phenergan injected intravenously 5 to 30 minutes before have no influence on the previously established responses to a constant dose of acetylcholine (see Graph. 4).

We have not been able to find that Phenergan increases the antagonistic effect of atropine against acetylcholine on arterial pressure as was demonstrated by Daniélopolu² in the case of Antergan (see Graph. 5).

(c) *Effects on the vascular response to adrenaline:* Our preparation allowed us to experiment only with quantities smaller than 1 mg/kg. It was, however, possible to observe



Graph. 3.

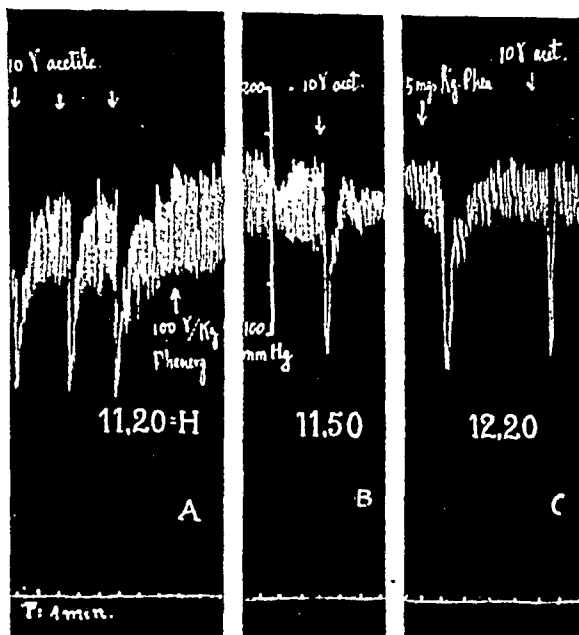
Cat of 2.950 kgs. Hypotensory effects of a single dose of intravenous Phenergan injected repeatedly at equal intervals and volume of injection, varying only the speed of injection. V: duration of injection. H: hour. T: time. (At C, momentaneous defect of the manometer's inscriptor.)

that even in the case of smaller doses Phenergan increases the depressor reaction of adrenaline (see Graph. 6).

DISCUSSION

The hypotensory effect of Phenergan in intravenous injection is found with all synthetic antihistamines in general.

The importance of the speed of injection as regards the extent to which pressure is lowered by antihistaminic drugs was proved by Loew et al.⁵ in the case of Benadryl and with greater precision by Winder & Thomas,⁷ who estab-



Graph. 4.

Cat of 2.400 kgs. Vagus nerves sectioned.

At A: stabilized responses of the A. P. to 10 γ acetylcholine and intravenous injection of 100 γ /kg Phenergan.

At B: response of A. P. to 10 γ acch. 30 minutes after the application of the antihistamine.

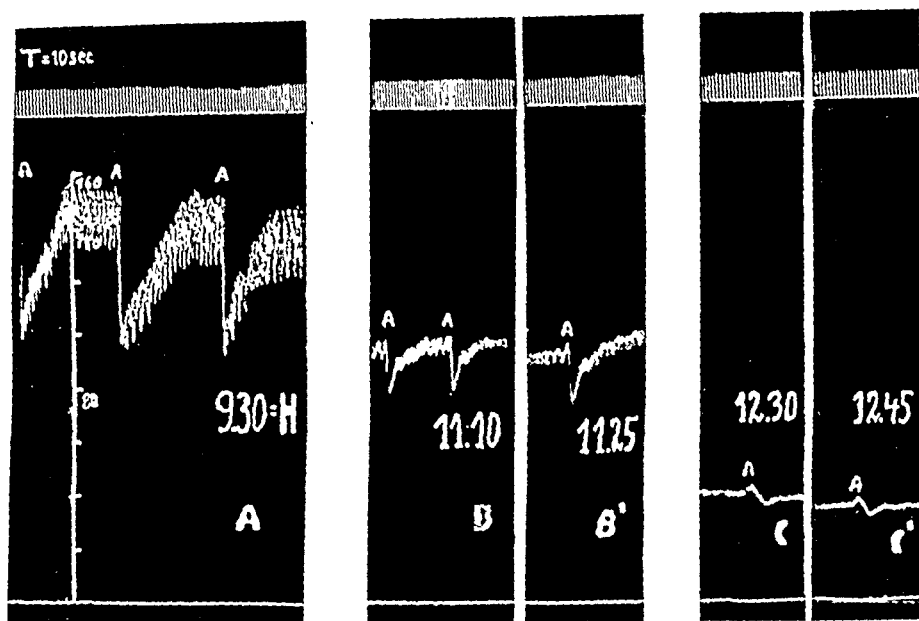
At C: hypotensory action of 5 mgs/kg Phenergan and response of A. P. to 10 γ acch. H: hour. T :time.

lished a relation between the extent of hypotension and the factor mgs/kg/min.

As regards the results given in section (b), it must be pointed out that it was possible to prove an effect contrary to the paralysing action of acetylcholine on the vascular fibre only in the case of Benadryl^{6, 7}. On the contrary, on the smooth intestinal fibre, as many authors have shown and also one of us³ on the striated muscle of the frog—in both

cases this quaternary base acts as an excitant—there is such an antagonism towards acetylcholine in a higher or less degree for all antihistaminic drugs.

The stimulation of the pressor action of adrenaline by



Graph. 5.

Cat of 2.350 kgs. Vagus nerves sectioned.

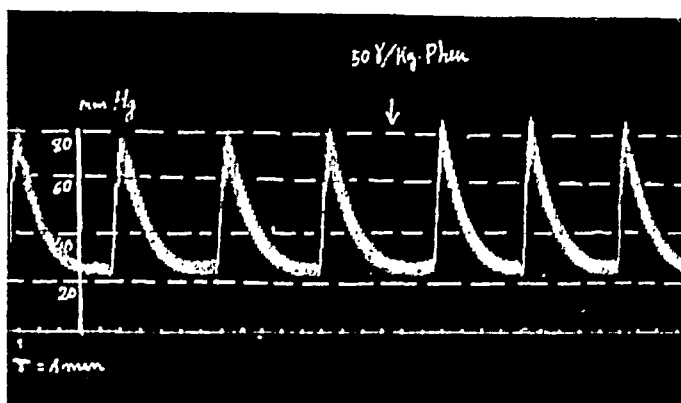
At A: stabilized responses of the A. P. to 10γ acetylcholine.

At B: responses of the A. P. to 10 γ acch. 60 minutes after hypodermic injection of 40 γ/kg atropine, and at B': response to the same dose of acch. 15 min. after intravenous injection of 5 mgs/kg of Phenergan and 75 min. after atropinization.

At C: response to 10 γ acch. 60 min. after a second atropinization by 150 γ/kg atropine, and at C': response to the same dose of acch. 15 min. after intravenous injection of 5 mgs/kg Phenergan and 75 min. after the second atropinization. T: time. H: hour.

the phenothiazinic compound that forms the subject of our study was also observed in the case of other antihistamine.^{1, 5, 6} The experimental technique employed by us (spinal cat), even though it did not allow us to work with larger quantities of Phenergan due to its hypotensory action, has the advantage of excluding all central influences from the possible causes of the phenomenon observed.

Among the several causes adduced by authors to explain potentiation of adrenaline effects by antihistaminic substances we should like to mention the very interesting interpretation given by Yonkman et al.⁸ to account for the stimulating effect of Pyribenzamine on some vegetative actions of adrenaline. These authors suppose that the antihistamine studied



Graph. 6.

Spinal cat of 2.500 kgs. Effect of 50 γ/kg Phenergan given intravenously on the stabilized responses of A. P. to 15 γ adrenaline. T: time.

by them would inhibit the action of aminoxidase or other enzymes related with the degradation of this hormone.

SUMMARY

In dialized cats an immediate depressing vascular action is proved for Phenergan (compound 3277 R.P.) given intravenously.

The importance of the speed of injection is noted in the extent of lowering arterial pressure by the antihistaminic drug.

Phenergan has no influence on the depressing vascular action of acetylcholine, nor does it stimulate the antagonistic effect of atropine against acetylcholine on vascular fibre.

In the case of the spinal cat the stimulation of the hyper-

tensory vascular action of adrenaline by small doses of Phenergan has been proved.

We wish to express our gratitude to Prof. F. G. Valdecasas for his advice and assistance during the course of this work.

Thanks are due to Dr. B. N. Halpern, Paris, for Phenergan.

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PRURIGO BESNIER (ATOPIC DERMATITIS) AND PRURITUS

By

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Besnier wrote about prurigo diathésique, the disease defined by him: "Le prurit est le symptôme premier et le premier symptôme", and this view that the itch is the primary symptom of prurigo *Besnier* is still maintained by dermatologists. It might therefore be imagined that the itch could occur without visible skin-symptoms, and that one could have a prurigo *Besnier* without skin manifestations, in other words a pruritus with the same etiology as prurigo *Besnier*.

With regard to this question I have gone through 1000 continuous records of my asthma cases, and from these picked out the patients who stated having or having had persistent or recurrent intense itch, as far as possible excluding urticaria, (20 patients whose infantile prurigo had disappeared before their second year, are not included).

Altogether it amounts to 98 patients, 2 to 60 years of age.

100 asthma-patients

Typical prurigo <i>Besnier</i> in 61 patients				
Atypical	"	"	"	25
Pruritus	"	12	"

As appears from the list 61 patients had "typical prurigo *Besnier*", by which I here understand prurigo localized to the hollows of elbows and knees.

"Atypical prurigo *Besnier*", that is prurigo localized to other regions than the flexures, was found in 25 patients.

The extent of the eruption in patients of this group varied a good deal. In some patients it was localized to neck, wrists, and ankles, places frequently attacked also in patients with typical prurigo Besnier, but in other cases it was even more locally confined; thus a boy had for many years had prurigo exclusively confined to the inside of both femora. But in some patients the eruption was limited to a still smaller part of the skin and did not even always occur symmetrically, as is usual in prurigo Besnier. One patient thus stated having an intensely itching eruption on three fingers of one hand every spring, in another every attack of asthma was preceded by an eruption on the back of his hands and in front of his ears. I do not know whether dermatologists will refer these skin complaints to prurigo Besnier, but at any rate they come under what is called atopic dermatitis.

No sharp line can be drawn between this group of patients with atypical prurigo Besnier and the next group of patients with pruritus. Most of the latter 12 patients had their itch exclusively or predominantly in immediate connexion with attacks of asthma. The itch in these patients varied in extension, but in each patient it was always localized to the same part of the skin.

A few patients stated that simultaneously with the itch they got a slight eruption of small papules on the back. In all the other patients, however, the itch appeared without the patients having noticed any eruption at all.

The itch might be confined to a very small part of the skin: Thus one patient got such an intense itch of both wrists during every attack of asthma that he scratched them till they bled; another stated that for ten minutes before each attack of asthma he had an intense itch of the chin.

Whether these cases of pruritus have the same etiology as prurigo Besnier, I do not know, but that they as well as prurigo Besnier have some connexion with the patients' asthma is at any rate certain. With these investigations I have only wanted to call attention to the fact that there seems to be

a very gradation from typical prurigo Besnier to pure pruritus.

SUMMARY

An account is given of the appearance of prurigo Besnier and pruritus among 1000 asthmatics. There seems to be a gradation from typical prurigo Besnier to pure pruritus.

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INHALANTS AS AN ETIOLOGICAL FACTOR IN PRURIGO BESNIER (ATOPIC DERMATITIS)

By

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Prurigo Besnier (or atopic dermatitis), which frequently occurs in patients who have asthma and hayfever, too, is generally regarded as an allergic disease, an interpretation which cannot, however, be regarded as quite settled as the decisive proof is still lacking. To be sure, it is often seen that a patient's prurigo is aggravated after the consumption of food allergens like eggs, fish, and others, but, this should be remembered, only during periods in which the patient has his prurigo, whereas nobody has ever succeeded in causing an outbreak of prurigo in patients in a period free from dermatosis (*Sulzberger & Goodman, Nordlind*). Strictly speaking, therefore, we can only say that there is a close connexion between prurigo Besnier and an allergic constitution.

In the American literature foods used to be regarded as the most important etiological factor in atopic dermatitis; but in recent years several writers, especially *Feinberg, Rowe* and, lastly, the Dane *Nexmand* have pointed out that airborne allergens play an essential etiological rôle in this disease. The allergens are supposed to be absorbed through the membranes of the respiratory organs and via the blood carried to the skin.

As the question is of fundamental importance and, as far as I know, has not before been discussed with a critical review

of the arguments advanced in favour of this theory, I have thought it expedient to take it up for discussion.

The arguments brought forward in favour of the view that inhalants play an essential part in prurigo Besnier are as follows:

(1) A number of writers have found that many prurigo-patients have positive cutaneous reaction to airborne allergens. However, no great importance can be ascribed to this as a proof of the inhalation-theory, because the positive reaction may be due to complicating allergic diseases. Thus when *Brunsting*, as cited by *Nexmand*, found positive cutaneous reaction in 32 % of his prurigo patients, this is certainly a very high figure; but as 34 % of the patients had hayfever, it is very likely that the positive reaction is due the patients' hayfever and need have no relation to the prurigo.—Out of *Nexmand's* 100 patients with prurigo Besnier 27 had also asthma or hayfever, and out of these 23 (85 %) had positive cutaneous reaction to inhalants; out of 67 patients of his with prurigo alone, only 14 (20 %) had positive reaction to inhalants (and 2 of these patients, who had positive reaction to pollen, suffered from rhinitis every summer, so that it is not improbable that they had hayfever, too). Apart from this, no material to my knowledge has been published about the frequency of cutaneous reaction in patients with uncomplicated atopic dermatitis.

(2) A fact which speaks for the importance of airborne allergens as an etiological factor is the influence of a change of environment on prurigo Besnier. Some excellent investigations into this have been made by *Nexmand*, who in a convincing way has proved that the prurigo may disappear completely on a sea-voyage, a journey abroad, or by removal from a damp house to a dry one. In all these cases the asthmato-genous allergens, fungi, house-dust, or animal-emanations seem to play a part; most of these patients were asthmatics, and at the change of environment the asthma-attacks disappeared simultaneously with the prurigo.

(3) The importance of pollen in prurigo Besnier has

been examined by *Feinberg*, *Rowe*, and *Nexmand*. It has been emphasized by these writers that patients with seasonal exacerbation of their prurigo in spring, summer, or autumn often have positive cutaneous reaction to pollen, and a number of them have also hayfever. However, I should like to call attention to the fact that exacerbation of prurigo in autumn seems to occur as frequently in Denmark as in the U.S.A., though autumn-hayfever plants are exceptionally rare in Denmark.

Still the fact that there is a connexion between prurigo and hayfever appears partly from the fact that many patients state that their prurigo is worst during the periods in which they have hayfever, and partly from the results of the desensitizing treatment, as patients who are kept free from hayfever in summer by a prophylactic treatment with pollen-extract also get relief from their prurigo, whereas patients whose hayfever is not improved by the treatment get no improvement of their prurigo either (*Sulzberger & Goodman*, *Nexmand*).

(4) Oddly enough, very few publications exist about experimental investigations with airborne allergens. An interesting experiment carried out a. m. Prausnitz-Küstner-de Besche has been made by *Sulzberger & Vaughan*: A healthy person was given an intracutaneous injection of serum from a prurigo-patient with allergy to silk, and 24 hours later the same person was made to inhale silk dust, by which a papular reaction was produced in the place where the allergy-serum had been injected, but not in the control place where normal serum had been injected.

The experiment is interesting, because it proved that the silk allergen had been absorbed through the respiratory organs and carried to the skin via the blood. But it does not afford a direct proof that the patient's prurigo was caused by the inhalation of silk, because the local reaction was a urticaria-papula and not a dermatitis.

A single clinical experiment has been made by *Zakon & Taub*, who made a prurigo-patient with allergy to horse-

dander sniff horse-dander with the result that a rhinitis developed and in the course of twelve hours the dermatitis was aggravated. But it is the only case I have been able to find in the literature—there may be others, but apparently they are rare. Perhaps in this connexion the few cases might be mentioned in which patients seem to suffer an aggravation of their prurigo at the smell of fish. Such cases have been mentioned by *Nexmand* and others.

(5) Finally there is a fact to which supporters of the inhalation-theory attach the greatest importance: the prurigo often occurs in patients with asthma and hayfever, and the prurigo is often aggravated in periods with asthma- and hayfever-attacks; in these cases it is assumed that the outbreaks of prurigo are due to the same allergens as are the cause of respectively the asthma and the hayfever attacks.

Thus *Feinberg* has published material dealing with 14 patients which is intended to prove the importance of pollen and fungus allergy in atopic dermatitis; nearly all these patients had asthma, hayfever, or rhinitis in summer; the same is true of *Figley & Pankhurst's* patients with silk-allergy; all patients had respiratory manifestations. Also by far the greater number of *Nexmand's* patients with exacerbation of their prurigo from inhalants had asthma and hayfever.

According to the existing publications, thus nearly all the prurigo-patients whose outbreaks of prurigo were caused by inhalants, seem to have had either asthma or hayfever; and especially *Nexmand* points out that the outbreaks of prurigo often run parallel to the asthma and hayfever attacks, and in this sees a confirmation of the inhalation theory.

However, it seems to me that this very fact, that nearly all the patients besides their prurigo had also allergic respiratory diseases, greatly complicates the question of the importance of inhalants as an etiological factor in prurigo. *Besnier*. For it seems to me that one must ask the question whether the occurrence of prurigo might not be *secondary* to the disorder of the respiratory organs, and whether it is not the patients' condition itself during periods of asthma

and hayfever that causes the outbreaks. At least this seems arguable to me, and I should like to mention some of the possibilities which I think should be taken into consideration.

Thus several writers have maintained that various internal and external factors play an essential part in the occurrence of prurigo-outbreaks; psychic traumas for instance, such as an examination, matrimonial conflicts, etc., can often cause outbreaks of prurigo. Moreover the functioning of endocrine glands may influence the course of the skin disorder, thus the prurigo is often aggravated in the premenstrual periods and may improve or be exacerbated during a pregnancy.

As regards the psychic factor there is no doubt that asthma- and hayfever-patients especially in the periods of attacks are often seriously psychically affected, and it might therefore be thought that this psychic condition might at least in some cases be the cause of the outbreak of prurigo.

With regard to the endocrine glands, we know very little about how these glands are affected in periods of asthma, and about the whole state of balance in the organism during these periods, but after *Moro & Keller's* investigations into parallergy we have reason to assume that something does happen during these conditions.

By parallergy these writers understand the phenomenon that a sensitized organism, especially during the development of an allergy or in a condition of allergic fluctuations, particularly easily and quickly reacts "unspecifically", i.e., reacts to another irritant than the allergen to which the organism has been sensitized, and this other irritant may be an allergen or a non-allergen.

Parallergy has especially been examined with regard to the tuberculin reaction. If thus a smallpox-vaccination is made on a tuberculin-negative child, the tuberculin reaction is found to become positive on the 9.-12. day, that is at the time when the allergy has reached its culmination, and this positive tuberculin-reaction remains for a period of varying length.

But *Moro & Keller* mention that parallergy may also occur in other cases of allergy. Thus they quote a case of cow's milk idiosyncrasy, in which the child before the emergence of the idiosyncrasy did not react to tuberculin, but after the emergence of the allergy developed a positive Pirquet reaction, which disappeared simultaneously with the cow's milk idiosyncrasy. According to *Moro & Keller* this hyperergy shows itself not only with regard to the tuberculin

reaction, but also with regard to other allergic or nonallergic irritants, even traumatic irritants.

In asthma and hayfever we have a sensitized organism and in the periods of attacks there are great fluctuations in the allergic condition of the organism, so that we might expect parallergic phenomena. It might therefore be thought that the prurigo was a parallergic phenomenon, and so a manifestation due to other factors than the allergens that caused the asthma and hayfever attacks. It might be a question of other allergens, but it might just as well be a question of non-allergic irritants. One must bear in mind that most of these patients had had prurigo for years *before* they got asthma or hayfever, and during these years, too, the prurigo was subject to periodic exacerbations caused by unknown factors. It is therefore conceivable that it was these "unknown factors" which exercised their influence particularly easily in the periods of asthma and hayfever and gave rise to parallergic manifestations.

The question of the etiological importance of inhalants in prurigo Besnier, would have been less complicated if we had been able to examine the effect of these allergens on patients with uncomplicated prurigo Besnier, but as mentioned above, such an examination is hardly possible, as the inhalants seem to play an etiological part almost exclusively in patients who have also asthma, hayfever, or vasomotor rhinitis.

It is possible that the inhalation theory is a useful working hypothesis, but it does not yet seem sufficiently well founded to be convincing. With these remarks it has been my intention to call attention to the possibility that other factors may play a rôle in the cases in which *apparently* we have a direct effect of airborne allergens, a thing which the believers in the inhalation theory don't seem to have taken in consideration.

SUMMARY

The question of the importance of inhalants as an etiological factor in prurigo Besnier is discussed. Attention is called

to the fact that possibly other factors than the airborne allergens may play a part in the cases in which these allergens are apparently the direct cause of the outbreaks of prurigo.

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EXERTION URTICARIA AND LACTIC ACID

By

GILLIS HERLITZ

Since 1921, when *Joltrain* called attention to the existence of a form of urticaria provokable solely by physical exertion, many cases of this disease have been recognized and described by various authors. The condition seems to have stimulated much interest, especially among physicians concerned with sport medicine (*Klaus*), who are inclined to believe that this phenomenon is connected with the cases of sudden death recorded in association with swimming or during the practice of some other sport. Various theories, in which especially acetylcholine is believed to play an important role, have been put forward to explain the pathogenesis of the disease. In the monographs the illness is assigned to the group "physical allergy" and is coordinated with urticaria provoked by physical factors such as heat, cold, and light. As far as I know, the disease has been described in this country only once before, when *Ask-Upmark* (1943) published a case of a 24 year-old man, who, after muscular exercise, developed urticaria, hydrarthrosis and infiltrations in the skin similar to erythema nodosum.

In the course of the last four years I have observed two cases of this illness and carried out a few tests on them.

Case 1. Girl, born 1934. Apparently non-allergic family. Pat. had always been healthy except that ever since childhood the ingestion of raspberries, pears, and sometimes of eggs, generally gave rise to a rash attended by itching. Since the autumn of 1942 cycling, running, or any other sort of physical exertion provoked a general, severely itching nettle rash of the arms, waist,

and medial surfaces of the thighs, with a concomitant reddening and swelling of the face. A swelling sometimes appeared also on the volar aspect of the elbows and on the medial surfaces of the thighs. The rash and the swelling generally lasted only an hour or so. If the pat. had exerted herself strenuously, fever ($39-40^{\circ}$ C) and cold fits developed regularly as soon as the rash had disappeared. After 1-2 days the body temperature returned rapidly to normal. On some occasions asthmatic breathing had also been recorded in connection with the appearance of the rash. In the beginning the rash and the swelling occurred about once a month, but later they appeared about once a week or even more frequently, and finally, as soon as she exerted herself at all. Bodily exertion was apparently the only causal factor of her condition, which did not seem to be affected or provokable by heat, food, clothes, climate, etc. She was a victim to these attacks both in summer and winter, at home and elsewhere.

The girl was admitted to the Children's Hospital at Linköping in Sept. 1944. Her general condition on admittance was apparently normal. Eosinophile cells: 4 per cent. After a run of 2-3 minutes in the open air she developed a typical urticaria in the above-mentioned surfaces but no edema was manifest.

As it was evidently a case of an endogenous allergen, I decided to initiate the investigation with intracutaneous tests on the intermediary metabolic products of the muscles. I commenced with lactic acid, which is formed in such large quantities during physical exertion that the amphoteric reaction of the muscles becomes acidic.

A saturated (70-80 per cent) lactic acid solution was diluted to 1:100 with a normal saline solution. A quantity of 0.1 ml. of this dilution was then injected into the back of the patient. Within 5-10 minutes the patient reached with a severe urticaria over the arms, thighs, and waist, a bright reddening and slight swelling of the face, and a swelling of the medial surfaces of the thighs. The girl recognized the symptoms immediately.

As the girl thus seemed hypersensitive to lactic acid, desensitization tests were initiated according to the following table.

On 14th Oct. the girl ran half an hour in the open air, an exertion that would previously have caused violent reactions with edema and fever. After this exercise, however, her face, arms, and thighs were only slightly erythematous but without

itching and without swelling. Neither did she develop fever. The patient was released that day.

25/9	intracutaneous injection of 0.1 ml. lactic acid			1:10000: no reaction.
27/9	"	"	"	1:1000 : very transient erythema of the arms and volar surfaces of the wrists.
29/9	"	"	"	1:1000 : no reaction.
1/10	"	"	"	1:500 : very transient erythema of the arms.
3/10	"	"	"	1:500 : no reaction.
5/10	"	"	"	1:200 : no reaction.
7/10	"	"	"	1:100 : slight erythema of the fore-arms.
9/10	"	"	"	1:100 : no reaction.
11/10	"	"	"	1:50 : slight transient erythema of the arms.

Lactic acid in concentrations exceeding 1:50 could not be administered because signs of a commencing necrosis began to appear at the site of the last injection. The desensitization tests were therefore discontinued.

In reply to a telephonic inquiry made in Dec. 1944 the disease was said to give the girl but slight trouble now in spite of the fact that she ran about just as much as she used to. *Strenuous* physical exertion, however, was still followed by a nettle rash, but only of a very mild and transient nature. The rashes were no longer accompanied by fever, and she had not been absent from school a single day since her release. Before hospitalization she was absent every week one or two days at a time on account of her illness.

In Dec. 1947 I examined the girl again. Her symptoms were still manifestable but were of the same mild character as immediately after treatment. An intracutaneous injection of 0.1 ml. lactic acid in 1:100 dilution in the fore-arm provoked a marked urticarial reaction which, however, was limited to the fore-arm thus treated. Tests with passive homologous transfer ad modum *Prausnitz-Küstner* were now performed and positive results were witnessed. 0.1 ml. of the girl's serum was injected intracutaneously into the left fore-

arm of a healthy person whose right fore-arm was at the same time given a subcutaneous injection of 0.1 ml. serum from another likewise healthy person. Twenty-four hours later an intracutaneous injection of 0.1 ml. lactic acid (1:100) in the sensitized area of the left fore-arm gave rise to a 10×14 mm. wheal surrounded by scattered erythematous patches, whilst a similar simultaneous injection of lactic acid given in the pretreated area of the right fore-arm produced no reaction at all.

Case 2. Boy, born 1931. Apparently healthy non-allergic family. Pat. had always been healthy and had never had allergic diseases. Since the early part of spring 1946, moderate physical exertion gave him a rash, first red and patchy, after which gnat-bite-like severely itching blotches appeared over the chest and the volar aspects of the arms. The blotches used to disappear after about half an hour's rest. The boy was not hypersensitive to any particular food-stuffs, nor had heat or cold alone ever given him a rash.

On 1st Oct. 1946 lactic acid tests were performed in the same manner as in Case 1. A quantity of 0.1 ml. solution (1:100) was injected intracutaneously into the left fore-arm. After about five minutes a 20×31 mm. wheal with a red circumferential zone, 50×70 mm., was observed. Immediately afterwards pronounced erythema appeared over the chest and the volar aspect of the fore-arms. The patient recognized the symptom immediately. The whole of the waist was markedly dermatographic. The erythema subsided after about 15 minutes, the wheal after a good half hour.

The following day *Prausnitz-Küstner's* test was performed in the same manner as in Case 1. The test gave a positive reaction with a 12×15 mm. wheal, whereas the control test was negative.

Desensitization was then initiated according to the following table:

3/10	intracutaneous injection of 0.1 ml.	1:10000: no general reaction but
	lactic acid	distinct local reaction,
		wheal 7×7 mm.
5/10	" " "	1:5000 : much weaker reaction
		than with 1:10000.
7/10	" " "	1:2000 : no reaction.
9/10	" " "	1:1000 : no reaction.
11/10	" " "	1:700 : no reaction.
15/10	" " "	1:500 : no reaction.
18/10	" " "	1:300 : no reaction.
22/10.	" " "	1:100 : no reaction.
29/10	" " "	1:100 : no reaction.

On 29th Oct. the boy began to take part in the gymnastic lessons at school again, a practice that had previously been impossible for him on account of the hives. After such lessons he now experienced only a slight itching of the chest but no rash.

On 15th Nov. 1947 the patient was re-examined. In the meantime he had been less troubled by his illness than before, but was not altogether free from it. A new test with an 0.1 ml. intracutaneous injection of lactic acid in 1:100 dilution produced a 12×15 mm. wheal surrounded by scattered red patches at the site of the puncture but did not excite a reaction of the skin elsewhere. *Prausnitz-Küstner's* test was repeated and gave also this time a positive reaction.

With a view to determining the lactic acid sensitivity of healthy individuals and persons with manifestations of allergy other than exertion urticaria, tests were performed on a number of children with eczema or asthmatic bronchitis and on healthy individuals with no manifestable or known symptoms of allergy. Every case was given an intracutaneous injection of 0.1 ml. lactic acid in 1:100 dilution. None of the sixty healthy individuals thus injected gave reactions exceeding that of a very moderate wheal and surrounding erythema. 70 per cent gave no reaction at all. Of 22 infants with eczema infantum about half reacted with a more pronounced wheal formation and surrounding erythema. Of 8 asthmatic children of various ages only one reacted, and then after about ten minutes with a rather violent attack of coughing, which lasted about 20 minutes. A second injection was given the following day and produced a similar reaction. Two grown-up women suffering from heat urticaria not elicitable by exertion did not react at all to the lactic acid test.

Desensitization tests were performed on all those eczematous infants that showed hypersensitivity to lactic acid, but no substantial changes were noted in the subsequent condition of the skin.

With reference to *Grant*, *Pearson*, and *Comeau*, who found that the local administration of choline derivatives

could provoke an attack in persons suffering from urticaria after emotion, exercise, and warming the body, a test was performed in Dec. 1947 with a subcutaneous injection of 5 mgm. acetylcholine in the present Case 1. No local or generalized urticarial reaction was observed. According to *Grant* et al. the effects of acetylcholine given subcutaneously are uncertain, but unfortunately the choline derivate they used, i.e. carbaminoylcholine chloride ("Doryl"-Merck), was unavailable at the time of the experiment.

Peter and *Silverman* were also unable to demonstrate a pure acetylcholine action in their case, neither were they able to reconstruct a pure histamine allergy. On the other hand, they could provoke urticaria if histamine phosphate and Furmethide (which is chemically related to acetylcholine and has an action which is similar to that of acetylcholine) were injected simultaneously into opposite arms of the patient. They therefore reasoned that the mechanism is complex and that an acetylcholine-like reaction and a histamin-like reaction are responsible and act together.

With their experience in mind simultaneous injections of histamine and acetylcholine were tried in the present Case 2. On 2nd March 1948 a quantity of 0.25 ml. (0.25 mg.) histamine ("Imido"-Roche), and 5 mg. acetylcholine (Roche), were injected into the superficial layers of the skin of the opposite arms of the patient. After 5 minutes there appeared a wheal 25×35 mm. and erythema at the site of the histamine puncture, whilst the acetylcholine puncture showed but a slight local erythema. No signs of urticaria were observed elsewhere, except perhaps on the shoulders, and there but faintly. In 2 healthy controls the histamine puncture provoked wheals 17×30 , and 24×32 mm., respectively, with surrounding erythema, but no urticarial reactions were noted on other parts of the body.

It is perhaps astonishing that such a simple substance as lactic acid can act as an allergen. It has generally been believed that the so-called endogenous allergens are pathologically changed proteins or high-molecular metabolic products

of such proteins. That lactic acid is able to produce eczema in bakers has been shown by *Kenedy*, and has apparently also been demonstrated by other workers (*Bonnevie*). *Schurch* tried several substances formed in the normal body (lactic acid, dextrose, β -hydroxybutyric acid, acetone, adrenaline etc.) on eczematous individuals and in one case he was able to provoke a reaction with β -hydroxybutyric acid, which is closely related to lactic acid, but he had no success with lactic acid. It seems, however, that *Schurch* performed percutaneous tests only.

SUMMARY

Two cases of exertion urticaria giving the patients considerable trouble were subjected to intracutaneous tests and found to be hypersensitive to lactic acid. Passive homologous transfer ad modum *Prausnitz-Küstner* gave a positive reaction in both cases. Desensitization with lactic acid given intracutaneously and in doses of gradually increasing concentration resulted in a considerable improvement of the condition of the two patients.

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THE TESTING AND DESENSITIZATION OF ALLERGIC CHILDREN

By

O. BRANDBERG and O. WILANDER

In the autumn of 1945 before the Swedish Society of Internal Medicine we presented the results of our tests and desensitizations of children suffering from allergic diseases, preponderantly asthma. We had then formed conclusions which seemed so encouraging as to be deserving of publication. Now two more years have passed and more material has been gathered together for closer study.

The method which we employ in our allergen treatment is more or less the same as that described on a former occasion (*Annales Paediatr.*, Vol. 166 No. 5 1946).

As a matter of routine about fifty allergen extracts are used. When the history or other factors provide grounds for suspecting some quite specific allergen, this is prepared. The extracts are produced by Dr. Wilander at the Central Laboratory of this hospital. In principle we follow Salén's method of treatment, with a preliminary desensitization ("rush sensitization") with allergen extract in rising doses, commencing with dilutions of 1 : 1,000,000 (or in very susceptible cases 1 : 10,000,000). Whereafter the doses are increased successively, if possible as far as undiluted extract. If local or general symptoms appear during desensitization (urticaria, asthma, etc.), we proceed with extreme caution and often begin treatment all over again with weak solutions. When desensitization is complete, allergen injections are continued once a month for at least a year.

Paper read at the First Northern Allergy Congress, Copenhagen, 9th September 1947.

In our previous investigation we found that of 28 allergics 20 were boys and 8 girls, about 40 % had had eczema in childhood, and about 60 % had an hereditary disposition for allergic diseases. Eosinophilia was inconstant, being absent in about 40 % of the cases. Most of the patients, about 60 %, reached to the house-dust test, a third to cat, cattle, fish or horse tests. There was considerable variation in the reactions. A distinct improvement was observable in about 75 % of cases. But despite this figure, 75 % improvement, we shall for many reasons regard our result critically.

In addition to the asthma cases, 26 of eczema (prurigo Besnier), rhinitis, conjunctivitis and urticaria were treated. Most of them were combined with asthma and therefore, from our point of view, were of more secondary interest. Among them, however, were 10 cases (i.e. between a third and a half) which are now free of their symptoms.

Among the asthma cases in the hospital were some which do not form part of this material. They are: 1) 5 patients who for no particular reason did not complete the treatment. Of these, two are not now troubled by their asthma and the other three are said to be much improved. 2) 3 patients showed no reaction to the tests. Two were treated with injections of sulphur "allergol" and one remained untreated. In none of these has there been any definite change in the condition. 3) 8 cases were diagnosed by us as bronchitis asthmatica. They were treated with autogenous vaccine. During the period of observation six of them have been symptom-free, while the other two have had asthmatic trouble in conjunction with acute respiratory infections. These cases of asthmatic bronchitis do not belong to this material, but they are of interest from a differential-diagnosis point of view.

Material. Consists of 56 asthma patients, 37 boys and 19 girls aged between 0 and 13 years, treated in 1944 (16 cases), 1945 (16 cases) and 1946 (24 cases).

Age in years

	Total	boys	girls	0	1	2	3	4	5	6	7	8	9	10	11	12 years
No. of cases	56	37	19	1	2	1	6	3	12	7	6	4	3	8		3

The high morbidity for boys is remarkable. It agrees with Winge Flensburg's figures, which show 63.8 % of boys; our figure is 66 %. The reason seems to be unknown, but may doubtless be referred to the usual high morbidity among boys.

On the subject of age distribution there is not much to be said. If the group 0-2 years is small, the reason is merely that asthma in these years is less frequent, apart from the fact that treating such young children is risky and therefore is only undertaken exceptionally. It often excites reactions which may be quite dangerous. Therefore we hesitate to subject such small allergics to tests and desensitization. In those cases where we do treat the child we have a priori (from the anamnestic particulars or from our own observations) discovered an allergen quite specific to them. The only baby in the material was a six months' old girl with so-called cow-milk idiosyncrasy, having proved to be hypersensitive to cow milk when weaning began. The allergic symptoms consisted of urticarial eruptions and respiratory difficulty, not unlike asthmatic breathing but perhaps mostly the result of oedema in the upper respiratory passages. Both parents of this child had allergic manifestations among their respective relatives. In this case desensitization was easily done. It was completed by means of our regular routine with injections of diluted cow milk in increasing doses, but also with milk by mouth in rising doses from one drop thrice daily via ml. doses to full dose. The treatment was completed in fourteen days.

In the case of infants of one or two years the indications for treatment were also clear. For the most part they were fish-sensitive, and asthma and eczema occurred in combination. The same may be said of children hypersensitive to vegetables and eggs. In other words, distinctly allergic reaction to important foods. In these cases the tests were confined to such allergens as were found to be of significance, side by side with control of the allergen vehicle.

Whenever a child had reached the age of three we generally carried out the full routine tests and desensitization. It is true that rather disagreeable reactions sometimes occurred even in the tests, somewhat severe attacks of asthma being the result.

These, however, could be mastered with the aid of adrenal injections and an injectable form of calcium. In cases where strong reactions were to be apprehended the tests were divided many times over, the site chosen being on the arm instead of the back, so that a tourniquet could be placed on the arm if the reaction were too violent.

With the method we have practised, it was possible in the majority of cases to complete desensitization without exciting unwelcome reactions. However, there were some instances of these from very small doses (at dilutions of 1 : 100 and even 1 : 1000). These reactions were either local (at the site of injection) or general (urticaria and asthma). Such cases were naturally treated with the utmost caution, and the preliminary desensitization ("rush desensitization") had to be spread over periods sometimes as long as three weeks, whereafter in many cases we considered it necessary to keep to more small doses for the monthly injections; we could then later, if necessary, do another "rush sensitization" in order to increase the allergen tolerance.

Treated cases of asthma.

Of the 66 cases treated for asthma in 1944-1946, satisfactory answers to our inquiries were received in 56 from the parents of the children.

As fig. 1 shows,

- 22 patients no longer have asthma, about 40 %.
- 34 " still have asthma, about 60 %.
- 25 " are much improved, about 45 %.
- 8 " are somewhat improved, about 15 %.
- 1 patient is not improved, about 2 %.

How much may be ascribed to the treatment and how much may be categorized as spontaneous healing are of course questions that are much too difficult to answer. According to investigations by Flensburg (1945), children treated unspecifically for asthma still have attacks in 54.7 % of cases. Our material shows that the asthma disappeared completely in about 40 %, whereas about 60 % are still having attacks. Thus in our material the number

of cases with persisting asthma is higher than in Flensburg's. This is disappointing, because in our investigation in 1946 we believed we had reasons for anticipating a good percentage of cures. We considered that about 75 % were considerably improved. However, it may be that *complete* freedom from symptoms may be asking too much. When we see the results from another aspect, it cannot but be encouraging to learn how much improvement was actually obtained in most cases. It is stated in about 45 % that the child is "*much improved*", a condition that is reflected in fewer and less severe attacks and in a reduced number of days of absence from school. If we venture to combine both results, "no longer asthma" and "much improved", we get a value of 84 % of favourable results obtained. In unspecifically treated cases Flensburg observed less frequent but equally severe attacks in 71 %, and milder attacks but of equal frequency in 58 %. In so far as one can rely upon relatives' reports of improvement, our result is good. When the report is "somewhat improved" there are grounds for being uncertain. The figure for this group, about 15 %, must be viewed very critically. We have a feeling of wishful thinking, or a semi-reluctant concession to us who treated the child, seeing that Flensburg states that only 10 % of the asthmatic children in his material became worse. Accordingly, in a way we are disposed to regard the number of "somewhat improved" cases as over-estimated and to think that among them are concealed some which are not improved.

DISCUSSION

To what extent far-reaching conclusions can be drawn from the results of our treatment we would not venture to say, any more than two years ago. Apparently one can never give a promise of a *complete* cure. An allergic will always remain an allergic, no matter what steps he takes. But it is reasonable to entertain hopes of some improvement at least in cases where very outstanding specific allergens are distinctly influential. A child acquiring strong allergic symptoms, for instance from fish, and when tested and desensitized with fish extract presents marked

reactions, will probably engender hope of improvement from specific treatment. Likewise, the aforesaid case of cow-milk allergy provides an eloquent example of how a successful treatment may turn out. The position is most doubtful in cases manifesting numerous reactions to tests. Then there is always reason for being sceptical about the result of desensitization. It is certain that many positive skin reactions stand in no relation to an equal number of exciting factors. It is therefore imperative to clarify the deleterious allergens by means of provokations tests, or at any rate through the anamnesis.

To some degree our results are also difficult to judge for the reason that allergic diseases in children have a certain tendency to improve as puberty approaches. However, they seem to be better than in published, unspecifically treated cases, even if reports by relatives as to improvement must be taken with a certain reserve. Allergics are neurolabile and easily influenced personalities. Nevertheless, if scepticism does not compel us to turn our backs upon specific desensitization, it is because there is the possibility of procuring an improvement and that these possibilities should be utilized in good time before the case becomes inveterate. It is therefore our opinion that specific desensitization should be tried on the allergic children. If not, the opportunity will be lost and, unless the condition improves spontaneously, the prospects of successful treatment will be less once the child has grown up.

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ALLERGY TO MOULDS IN SWEDEN¹

A Botanical and Clinical Study

By

IVAR NILSBY

About 75 years ago the hypothesis that mould spores could develop hay fever and asthma was suggested by the English doctor *Blackley*. He himself suffered from hay fever and used himself as the experimental object in that he breathed in various "materials" and recorded how he reacted to them. Among others he breathed in moulds, both *Chaetomium* and *Penicillium glaucum*. About the latter experiment he writes: "The spores of the microscopic fungi (*Penicillium glaucum*) I have reason to believe will, when brought into contact with the respiratory mucous membrane, generate symptoms not unlike those of hay fever in some respects, but differing materially in others—being much more like those of ordinary influenza." It was not, however, until 1925 that anybody returned to the mould spores as the etiological agents of allergic diseases. The Dutchman *Storm van Leeuwen* had noticed that asthma was more prevalent in damp and low lying places in Holland than in more highly situated and dry areas. He considered that this depended on the fact that asthma developing miasms were found in the air of which the most important ones were mould spores.

¹ In abbreviated form this manuscript has been presented as a lecture before the Swedish Allergy Society.

Even to *Storm van Leeuwen's* investigations little attention was paid in the beginning. Even though occasional reports of mould allergy appeared in the literature, it was not until the investigation of the American *Feinberg* during the years 1935-1946 that general interest in this question was aroused. *Feinberg* made systematic analyses of the spore content in the air and also used the results of these investigations clinically. In his monography 1946 he presents a large amount of clinical material, in which mould allergy has been the redeeming cause of the patient's ailment. *Feinberg* soon got followers in the whole of America and even in Europe.

It has been shown that mould spores are found in the air practically everywhere. The spore content may vary rather much, within some land areas there are evident seasonal variations, but above all there is a significant qualitative difference. Thus in Chicago *Feinberg* found that *Alternaria* and *Hormodendrum* were the dominating mould types while in Rio de Janeiro *Parsarelli* chiefly found that *Penicillium*, *Hormodendrum* and *Aspergillus* were the commonest, while *Alternaria* was the rarest.

The first step in the study of mould allergy in Sweden was therefore to obtain information about the spore flora. No such investigations were available when this work was started. The Danish botanist *Rostrup* had in 1908 investigated the spore content in the air of Copenhagen and vicinity. *Nexmand*, who had investigated mould allergy of patients with prurigo Besnier had, in connection with this work, made spore analyses in dust from the homes of these patients. Further *Flensborg* and *Barfod* had isolated some mould types from the homes of children suffering from asthma.

During the work's progress it appeared that similar investigations had been carried out simultaneously in Sweden by *Rennerfelt* and in Denmark by *Flensborg*.

During the summer of 1946, a systematic analysis of the air's spore content with special attention to the following questions was started. To what extent do mould spores occur in the air? Is the content of such spores so high that they

need be considered the allergy factor? Which mould spores are the most common? How do the variations appear during different seasons? Is there any difference in spore content in and out of doors, in town and in the country?

Technique.

Two different methods are available for these analyses.

1. *The slide glass method.* These tests were carried out in the same manner as pollen analyses. A slide glass covered with liquid paraffin or glycerin was exposed for 24 hours whereupon the number of spores was counted. The advantage of this method is that good quantitative information of the spore content of the air is obtained. The disadvantage is, however, that one cannot obtain an exact report of which kinds of mould spores are concerned since no more than a few spores can be distinguished morphologically.

2. *The Petri dish method.* Petri dishes with a diameter of 9 cm. and containing a suitable nutrient were exposed for a certain time. In a few days the spores germinate and one can systematically determine the spore colonies formed.

Only the Petri dish method has been used in my investigations. Its great advantage is that one obtains an idea of which mould spores are present in the air. The disadvantage is that one only records the spore content during a small part of the day. Fig. 1 demonstrates that the spore content of the air varies a great deal during the day, a fact that has been pointed out by *Blumstein* and others. However, if one makes daily observations over a long time, a rather good survey of the spore content is obtained.

A modification of Sabouraud's agar has been used as nutrient medium in the Petri dishes.

Aminosol-glucose	5 ¹
Agar	2
Aq dest ad	100
Buffered to pH 5.3	

The spores have been allowed to develop at room temperature and the

¹ Aminosol-glucose = 20 per cent protein-hydrolysate and 80 per cent dextrose).

plates have been observed up to 14 days. Most of the colonies have developed in 5-7 days, but certain types require longer time. We have also made experiments wherein dishes were placed in the thermostat at 37° C., but it was shown that at this temperature only certain colonies developed. *Hormodendrum* does not grow at all at 37° C. and it seems as if one day in the thermostat at 37° C. is sufficient to kill these spores. Certain types of *Penicillium*, *Mucor*, and *Aspergillus* grew better at 37° C. than at room temperature.

The examinations of the spore colonies have been made with the help of Gilman's flora of fungi, special attention being paid to the microscopic appearance of the colonies, to the forms of the hyphae and the formation and morphological structure of the spores.

The Mould Spore Content of the Air of Oerebro.

Oerebro is a medium sized Swedish city of about 60,000 inhabitants, situated in lat. 59° north inland with rather distinct inland climate. The city itself is situated on a plain at an altitude of 28 m above sea level. The plain stretches about 10 km in all directions and is bounded by rather large forest areas chiefly containing evergreens with a scattering of birch. Lakes and waterways are rather numerous near the city and in its surroundings. The average temperature of the year is + 5.4° C. with July as the warmest month (aver. temp. + 16° C.). February is the coldest (aver. temp. — 3.3° C.). The rainfall is 611 mm, July and August being the months with the greatest rainfall. The humidity is about 80 per cent. The duration of the snow-covering is about 90 days.

Outdoors.

Petri dishes were exposed on a balcony situated in an open area in the city's outskirts. Daily exposures were made between the times of August 1946 and December 1947. The exposure time was 30 minutes. Weather conditions were recorded in order, if possible, obtain some correlation between these and the spore content in the air.

It was found that the spore content of the air changes very much from day to day. It has already been pointed out in the introduction that we have rather large variations even

within a given day. In order to get somewhat more comprehensive picture of changes of the spore content of the air I have therefore calculated the average count of spores per plate per week. See fig. 2.

One finds rather a marked seasonal variation in the count of air-borne mould spores. The spore content begins to climb markedly at the conclusion of May and the beginning of June and remains constant on a rather high level until the end of October. Between November and May we have few spores in the air, but in spite of the severe cold with temperatures ranging as low as -15 to 20° C. for several weeks the spores do not completely disappear. Since the spores do not generally require more than 5 days to mature and form new spores only a short time of favourable growing conditions (warmth, humidity) is needed to obtain an increase in the spore content even outside the usual season. Such an extra peak was recorded in the autumn of 1946 in connection with unusually humid and foggy weather.

It was found that certain mould types show a strong seasonal variation while others occur with approximately the same frequency throughout the year. *Hormodendrum* shows the most noticable seasonal variation while *Penicillium* does not show any seasonal variation during the year whatsoever. *Feinberg* has pointed out the same fact.

If we consider the total count of types of colonies recorded we reach rather significant values during the mould season. 50 colonies on a plate exposed for 30 minutes is not unusual. We have thus to calculate with a rather high spore content during the mould season.

If these results are compared with *Feinberg's* figures, it is found that the mould spore content shows good agreement quantitatively. Qualitatively, however, great differences are observed. The most noticeable difference is that *Alternaria* occurs in over 40 per cent in America and here only in few colonies. (See Table 1.)

In comparison with *Rennerfelt*, who recorded the mould-spore content outside Stockholm, we find a very good agree-

ment. If finally my data are compared with the results of the analyses of the mould-spore content in Denmark, which were made by *Flensburg* and *Samsøe-Jensen*, a qualitatively good agreement is found. These investigators, however, obtained rather much higher values for the spore content during the mould season. A possible explanation of this, suggested by

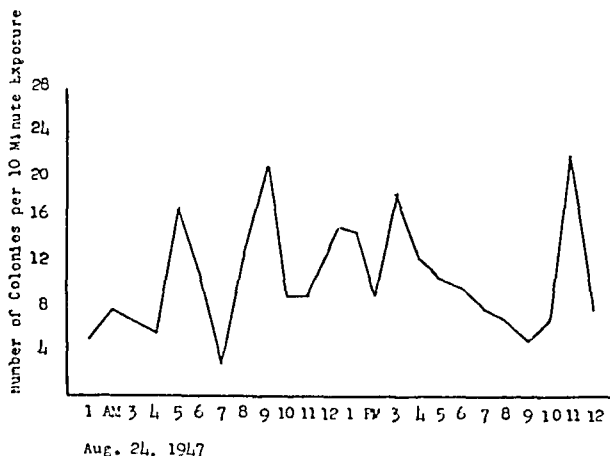


Fig. 1.

The changes in the spore content of the air during a day. One plate per hour during the 24th of Aug. 1947. Weather conditions: No wind, fair, temperature min. 12° C., max. 22° C.

these authors, is that Örebro has a drier inland climate than Copenhagen.

What influence do the weather conditions have on the spore content? The season variation itself of course is influenced by the type of climate prevalent in the country. The spore content is highest during the warm season. It climbs rather rapidly at the budding of the leaves and sinks to low values immediately after the falling of the leaves. The reason for these large changes from day to day during the season could not be determined. There was no correlation with the wind direction, the air temperature or the overcast. However, it was found that there was an increase in spore sedimentation on the plates during a strong wind and above all during foggy weather. (See fig. 3.) Further, compare the spore content in clouds. (See below.) This observation is probably

true about all air-borne particles and has been pointed out by *Flemming* in 1908 with regard to bacteria. Thus he has shown that the bacterial content in the atmosphere is particularly high at the level of the lower cloud limits. This may be due partly to the removal of bacteria from rising air currents by cloud formation.

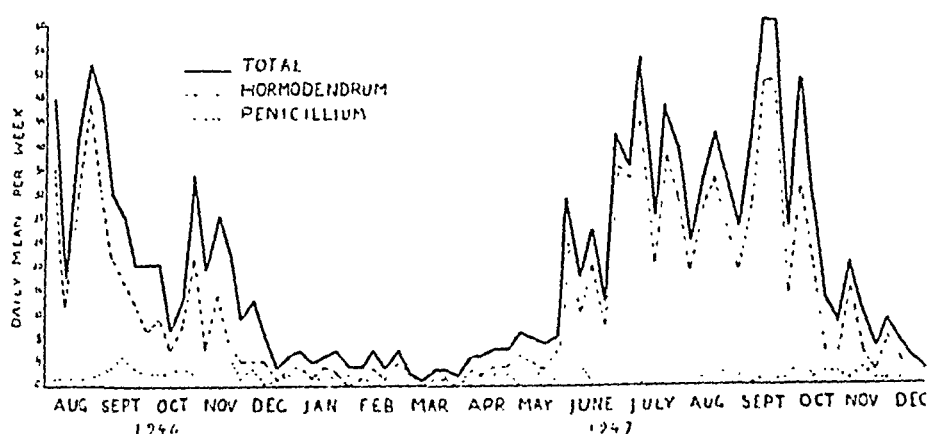


Fig. 2.

Content of mould spores in the air at Örebro (August 1946-December 1947).

In order to find out whether there was any difference between the city and country side, plates were exposed both in Örebro and outside the city to an extent of at least 10 km. No difference was found either qualitatively or quantitatively. See fig. 4.

Indoors.

Plates have been exposed in various homes and industries and considerably varying numbers of spores have been found. In dry and hygienic dwelling-quarters, and for instance in the rooms of Örebro Hospital few different colonies per plate exposed for 15 minutes were found. The average value for a great number of such exposures was 5 colonies per plate. In homes where complaints had been made to the Bureau of Health about the mouldy conditions of the home on the other hand an average value of 55 colonies per plate was registered.

TABLE I

Total Mould Colony Counts Aug. 1946-July 1947, Örebro, Sweden.

Outdoors			Indoors		
Genus	No. of Colonies	%	Genus	No. of Colonies	%
<i>Hormodendrum</i>	3,203	68	<i>Penicillium</i>	818	43.5
<i>Penicillium</i>	519	11	<i>Hormodendrum</i>	518	27.5
<i>Pullularia</i>	311	6.6	Yeast-like ¹	194	10
Yeast-like ¹	168	3.6	<i>Aspergillus</i>	116	6.2
<i>Botrytis</i>	72	1.5	<i>Pullularia</i>	106	5.6
<i>Aspergillus</i>	62	1.3	<i>Mucor</i>	53	2.8
<i>Alternaria</i>	26		<i>Alternaria</i>	40	2.1
<i>Mucor</i>	22		Miscellaneous	24	
<i>Trichothecium</i>	20		<i>Botrytis</i>		
<i>Phoma</i>	16		<i>Phoma</i>		
Miscellaneous	22		<i>Trichothecium</i>		
<i>Monosporium</i>			<i>Helminthosporium</i>		
<i>Helminthosporium</i>			<i>Scopulariopsis</i>		
<i>Scopulariopsis</i>			Myc. sterile and un-		
<i>Stemphylium</i>			known	18	1.0
<i>Spondylicladium</i>					
Myc. sterile and un-					
known	274	5.8			
Total	4,715			1,887	

Often it could be shown that a certain home had a particular type of mould. For instance in one home 25 colonies of *Alternaria* were found on one plate, a type of mould that is very rare in this country. In another home a pure culture of *Monilia tropicalis* was found, which is only sporadically encountered. Often a certain species of *Penicillium* in pure culture was observed, in one case 70 *Penicillium* colonies of the same species were observed on the same plate.

In different industries and working localities a rather variable spore content was found. The working places richest in spores were the greenhouses with an average of 80 colonies per plate exposed for 15 minutes, together with fruit in-

¹ Including *Monilia*, *Torula* and *Saccharomyces* spp.

dustries with 50 colonies per plate. Very high values were found upon investigating barns and other buildings in the country, with an average of 600 colonies per plate. During threshing or the stirring up of hay and straw we found hundreds of colonies even though the plates were exposed for only a few seconds.

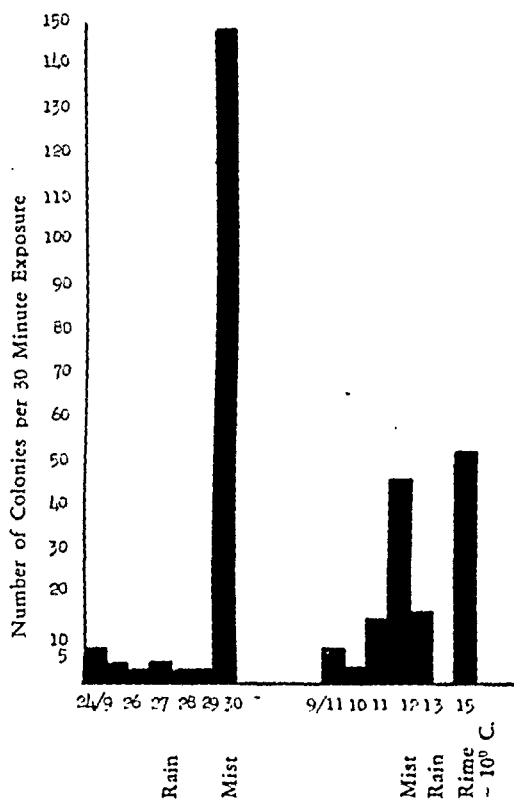


Fig. 3.

The Spore Content of the Air in Fog.

If those types of mould that are present indoors in homes are compared with those found outdoors a certain difference is observed. See Table 1. *Hormodendrum* is the most common mould type outdoors, while *Penicillium* is the most common type indoors. Furthermore *Aspergillus* and *Mucor* are significantly commoner indoors than outdoors.

Is there any difference between the spore content in larger and smaller cities?

Plates were exposed at the same time in Stockholm, Gothenburg, and Örebro. Stockholm and Gothenburg are both relatively large cities with about 675,000 and 325,000 inhabitants, respectively. All of these three cities are upon ap-

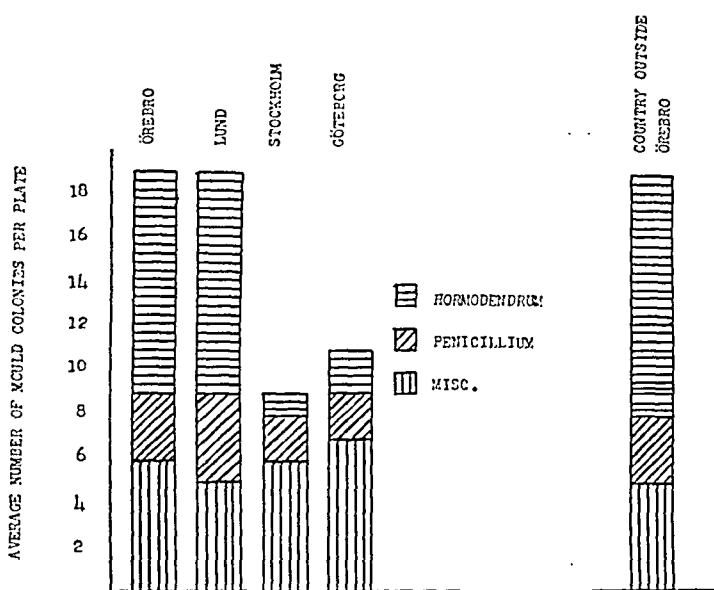


Fig. 4.

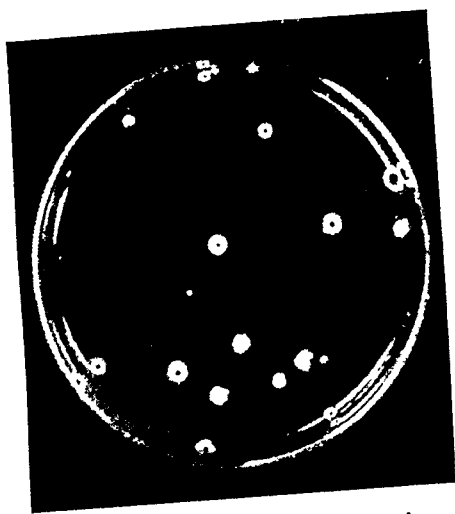
The number of air-borne fungi in larger and smaller cities and in the country.

proximately the same Northern latitude. However, Örebro is located in the inland. Stockholm and Gothenburg are coast towns, Stockholm being on the East coast and Gothenburg on the West coast. Even though Stockholm is on the coast the climate is drier than at Örebro. The rainfall of Stockholm is 569 mm per year, at Örebro 611 mm. Gothenburg has the greatest rainfall, viz. 738 mm per year. In all these places there is the greatest rainfall in the autumn.

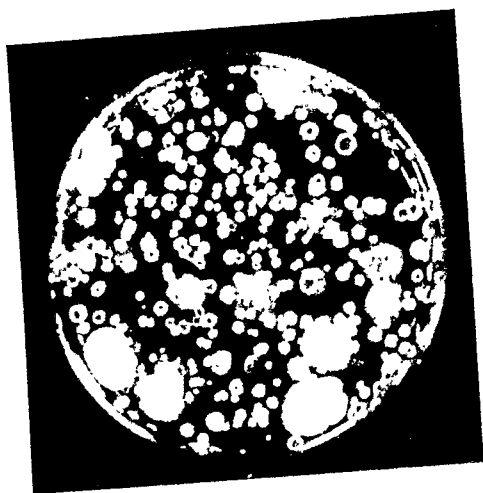
The result of the investigation is shown in fig. 4. There is a difference both quantitatively and qualitatively. A smaller number of spores occurs in the cities of Stockholm and Gothenburg. The main difference is that *Hormodendrum* is not

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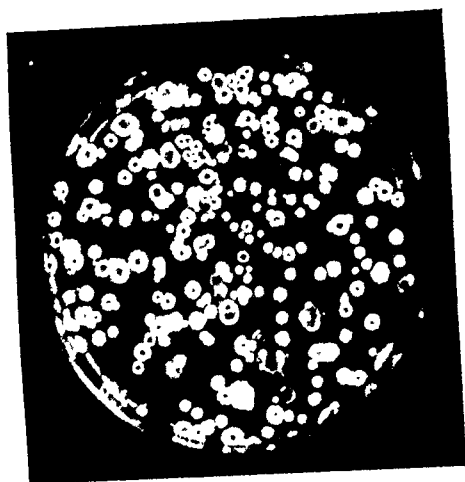
so common in these cities. The other kinds of mould do not show any significant difference. A similar result has been published in America by *Harris*, who has recorded the spore content at Cleveland, a city of about the same size as Stock-



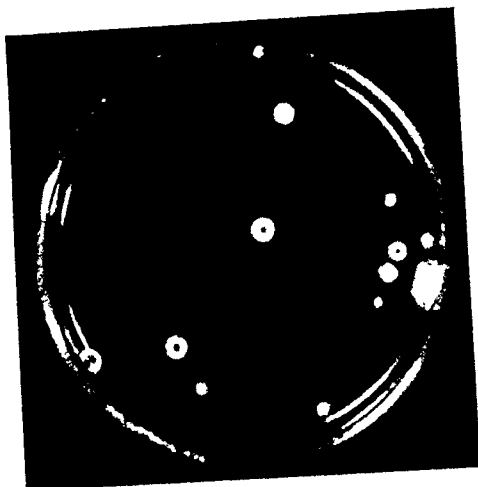
400 m. height. Ascending. Fair.



500 m. height. In clouds.



600 m. height. In clouds.



400 m. Descending. Fair.

Fig. 5.

Plates exposed from an airplane flying over Örebro the 19th Oct. 1947, showing the extraordinary collection of spores in the clouds.

holm, and in a small town 25 miles from there. He found at Cleveland a smaller number of *Hormodendrum* and *Alternaria* and a somewhat higher number of *Penicillium* and *Aspergillus* than in the country town.

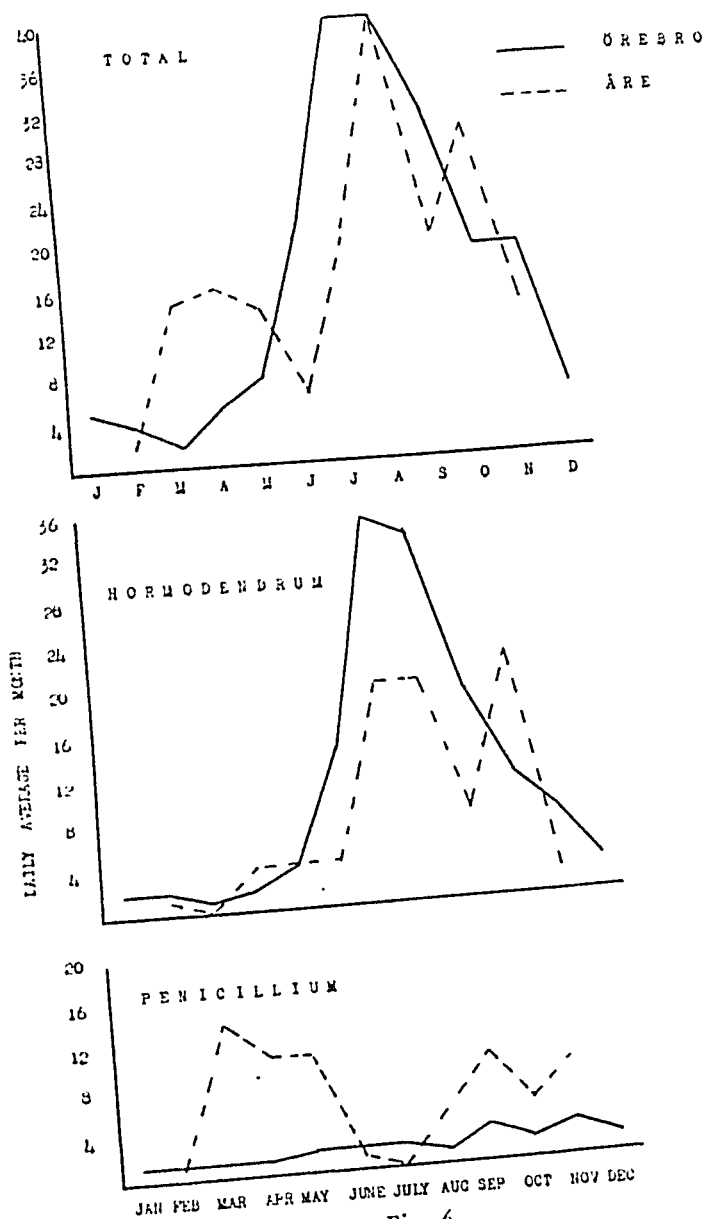


Fig. 6.
A Comparison of Atmospheric Moulds through the Year between Örebro and Åre.

TABLE 2
The Spore Content in Higher Layers of Air.

	Height in m	Number of colonies per plate
Flight the 8th Nov. 1946, Oerebro.	50	30
Wind W 3 sec. m. Fair. + 2° C.	100	7
Local clouds at 300 m height.	200	7
Flying speed 145 km/hour.	300	2
Plates exposed for 30 sec. 90 degrees angle to the flying direction.	300 (in cloud)	65
	500	2
	700	1
	1000	0
Flight the 9th Oct. 1947, Oerebro	50	50
No wind. + 3° C. Clouds 400-600 m.	150	50
Flying speed 145 km/hour.	200	52
Plates exposed for 30 sec. 90 degrees angle to the flying direction.	300	21
See fig. 5.	400-500 (starting clouds)	250
	500-600 (clouds)	225
	600 (clouds)	200
	400 (fair)	12

The spore content at different heights.

Plates were exposed from an airplane flying at different heights. The flights were made over Oerebro. The results are shown in Table 2 and fig. 5. The mould-spore content decreases with increasing heights up to 1000 m. Occasionally, however, spores may occur at still higher levels. Such investigations have been made previously, first by *Dillon Weston* in 1929 and later by *Proctor* and *Mac Quiddy*. The latter investigators recorded the occurrence of mould spores up to 7,000-10,000 feet.

The most interesting observation of this experiment was the extraordinary collection of spores found in the clouds. As a possible explanation it might be postulated that the mould spores are carried along with the rising air currents and when

TABLE 3

The Spore Content of the Air on Different Levels of a Mountain Åre.

	Total Number of Colonies per plate exposed for 30 minutes						
	1947			1948			
	23/9	6/10	5/11	22/5	24/6	10/7	21/8
The top of the Åre Mountain							
1419 m above sea level	4	41 (storm)	0		2	1	
Mörvikshummeln							
890 m above sea level	2		0	7		1	14
Timber line							
750 m above sea level	5		1			33	71
Meteorological station							
450 m above sea level	16			13	4	6	40
Åre Railway station							
378 m above sea level	16	6	8				

the moisture in these currents is condensed the mould spores adhere to the fine water particles; cf. conditions during fog.

Comparison between places at different latitudes.

Plates have been exposed simultaneously at Örebro and Lund which is a small town in the Southern part of the country, situated appr. in lat. 56° north. As shown in fig. 4 no difference could be recorded either quantitatively or qualitatively in the mould spores. That was not either to be expected in advance, since there is no great difference either in the climatic conditions or the vegetation in these two places.

A comparative investigation of the spore content of the air at Örebro and Åre is, however, of greater interest since Åre is situated in the Swedish mountain area in lat. 64° north and has a significantly colder climate. The average temperature during the year is $+1.5^{\circ}$ C. The warmest month is July with an average temperature of $+13.2^{\circ}$ C. and the coldest month is January with -8.9° C. The duration of the snow-covering is about 200 days, the first snow falling

TABLE 4
Mould Sensitivity in Various Allergic and Possibly Allergic Diseases.

Diagnosis	Number of tested cases	Positive skin reactions to mould extracts
Asthma bronchiale	75	14
Bronchitis asthmatica	59	7
Rhinitis chronica	69	7
Rhinitis allergica	9	3
Urticaria	17	4
Eczema	32	3
Conjunctivitis	15	3

around the first of October and a more permanent snow-cover usually appears about the 20th of November. The cultivated area here is very insignificant. The vegetation consists of evergreen forest with a scattering of birch. The timberline extends some 100 metres above the cultivated area. The comparative investigations of Örebro and Åre were made during a whole year.¹

The plates have been exposed at Åre's meteorological station, which is situated 450 m above sea level.

The results are presented in fig. 6. It was found that the total count of mould spores does not differ significantly between the two places. The spore season is somewhat shorter at Åre, which is alone due to the shorter summer season there. Qualitatively it seems as if a certain difference should exist. *Hormodendrum* is not so common at Åre as at Örebro, while *Penicillium* is commoner at Åre.

The spore content at different heights on Åre mountain has also been recorded. The result is presented in Table 3. The spore content decreases the higher one passes up the mountain. However, spores have even been found on the top of the mountain 1419 m above sea level, as was demonstrated by the fact that no less than 41 colonies developed on a plate exposed there during a storm on the 6th of October 1947.

¹ I offer my best thanks to chief physician V. Hedström, who has exposed all the plates in Åre and has shown great interest in these investigations.

TABLE 5

*The Strength of the Reactions to Different Types of Mould Allergy
(150 Patients).*

The strength of the reaction	+++	++	+	Total
<i>Hormodendrum</i>	15	40	8	63
<i>Penicillium</i>	8	33	11	52
<i>Mucor</i>	15	45	7	67
<i>Botrytis</i>	23	52	8	83

+++ = reaction = histamin (besides usual control we have also used histamin control upon testing).
 ++ = wheal + skin redness.
 + = evident skin redness.

Clinical.

The spores of mould fungi develop allergic reactions in the same manner as pollen. They are smaller than pollen and thus can easily remain suspended in the air and go far down in the bronchial system. Most of the mould fungi concerned are plant-saprophytic and apatogenic for men. The analyses of the spores made show that there is a sufficient amount of spores in the air to develop allergic diseases.

TABLE 6

The number of patients, who have reacted pos. to 1 species of mould	66
" " " " " " " " 2 " " "	66
" " " " " " " " 3 " " "	16
" " " " " " " " 4 " " "	2

In certain cases mould allergy may be suspected from the anamnesis. Thus the patient has often trouble during the summer, but these troubles draw out beyond the actual pollen season, which is evidently due to the fact that there is a large spore content in the air right into the autumn. This is especially true if the patient is sensitive to the mould types associated with a season. Should the patient be sensitive to those mould types which are not season-associated or has plenty of mould spores at home or at the working place, allergy difficulties may of course extend over the whole year. Often it is observed

TABLE 7
*Association of Positive Skin Tests to Mould Extracts with Those of
 Other Allergenic Substances.*

Positive skin reactions to mould alone	20	pat.
" " " to mould and other inhalants (net dust)	16	"
" " " to mould and dust only	8	"
" " " to mould, dust, and other inhalants	92	"
" " " to mould, dust, and food	14	"

that the patient has increased difficulties in air which is strongly mould containing, for instance in a barn during threshing. The difficulties are also usually accentuated during foggy weather. Occasionally it may be observed that the patient is sensitive to other fungi, for instance mushroom or yeast.

TABLE 8
Skin Reactions to Different Penicillium Species.¹

	I	II	III	IV	V	VI	VII	VIII	IX
B. N.	—	++	+++	+++	+	+	—	—	—
B. L.	—	—	—	++	—	—	—	—	—
A. H.	+	+	—	++	—	—	—	—	—

In order to find out how often positive skin reactions for the mould types here described are obtained extracts were made which were used in the testing both of confined patients with hay fever and asthma and of polyclinical patients with allergic diseases. The extract was made on all spore families previously mentioned but after a while the test was limited to the 4 most common (*Hormodendrum*, *Penicillium*, *Mucor*, and *Botrytis*), and only in special cases the patient was tested with all mould extracts.

¹ Species received from various asthma patients' homes. Docent Rennerfelt, Experimentalfältet, has tried to analyse the different species. II = *P. expansum*, V = *P. luteoviride*, VII = *P. flavoglaucum*. I = *Monoverticillatae*, II-IX = *Biverticillatae*, of which II, VI, VII, VIII, IX asymmetrical, III, IV, V symmetrical.

The preparation of the extract has been made according to *Feinberg's* instructions. A number of Erlenmeyer flasks with a suitable medium¹ are inoculated with the mould type from which one wishes to prepare the extract. When the mould colonies have developed to a thick mat and the spore formation has reached its maximum which may take from one to several weeks, the medium is filtered off. The mould is then transferred to 95 per cent alcohol for 48 hours during which time the spores are killed. Then the alcohol is poured off and the pellicles are dried. Thereupon the dried material is ground up and is now ready for extraction. The extraction is carried out in Coca's solution, first by shaking for 3-4 hours, then the solution is permitted to stand for a day, and afterwards is filtered. The filtrate is brought up to the boiling point once a day for 3 consecutive days, whereupon a sterility check is made.

The strength of the extract has been calculated in respect to the original mould weight after drying. We have had a 5 per cent solution (1 : 20) as a stock solution. For testing this stock solution is diluted to 1 : 2000.

There has been a great deal of discussion concerning the best method for determining the strength of an extract. This is due to the fact that we do not know what in the allergen is the active substance. Several authors maintain that we may obtain many different strengths of the extract upon as of a gravymetric standard. Cooke recommends instead the protein nitrogen standard for allergen extracts since the activity of an extract was generally found in the protein-fraction. The only reliable test for strenght of extract, however, is the biological test, which is very difficult to carry out in practice.

Before use the extracts are tested on healthy non-allergic persons in order to determine whether the extract as such is irritating. Upon testing 25 student nurses one reacted positive for two extracts (*Penicillium* and *Hormodendrum*), but upon further inquiry into her case history it was shown that she had had hay fever as a child but that she had had no further difficulties from that during later years. All others were completely negative for the extracts.

¹ Distilled water 5,000 cc. Sodium chloride 25 Gm.
 Peptone (Armour) 50 Gm. Meat extract (Armour) ... 25 Gm.
 Autoclave. Filter. Add maltose 100 Gm. Autoclave in large flasks.

The mould extracts have been tested with intracutaneous tests on all allergic patients who have been treated in the Medical Department from Oct. 1946 to Sept. 1948 in connection with the routine testing which patients undergo. The author has made the test himself except for the last year, 1948, when the laboratory chief, Dr. Wilander, made these tests. The persons consisted of 123 cases (many had not only asthma bronchiale but also hay fever). If the patient was treated more than once during the above period it is reckoned, of course, as one case. Of these 23 or 18 per cent have reacted positively for one or several mould extracts.

In order to get an idea of the hypersensitivity of mould in an average group of allergic or supposedly allergic patients I have included here the result of testing at the Central Laboratory. The patients come to the laboratory upon recommendation of various practitioners and the testing is carried out by the chief of the laboratory, Dr. Wilander. In many cases the allergic reactions are very improbable when studied from the point of view of the anamnesis; hence the figures obtained are not representative of purely allergic patients.

Between October 1946 and December 1947 about 1250 patients have been tested and of these 127 (10 per cent) have reacted positively to one or more mould types.

Table 4 shows how mould sensitivity is distributed within various allergic and possibly allergic diseases. These data include patients at the Central Laboratory during the period October 1946-April 1947. As might be expected, the relatively largest number of allergies were obtained among the patients with asthma and hay fever.

Table 5 shows the distribution of the skin reaction of the tested mould types and the intensity of the reactions.

It is found that the number of positive skin reactions is distributed rather evenly among the various types of mould. The least number of reactions and the weakest ones, however, are noticed for *Penicillium*. This is probably due to the fact that the genus of *Penicillium* includes many species and there

might be a pronounced species specification in the reactions of hypersensitivity. Compare the discussion at the end of this paper. Our extract of *Penicillium* is a mixture of a few different species.

Table 6 shows to how many kinds of mould the single patient reacted. It is found that the patient most frequently reacts to one or two different kinds of mould, rarely to all the four of them.

In order to determine whether there was any correlation between the types of mould to which the patient reacted and the types of mould in his surroundings, every patient was given two Petri dishes to put in the home and the workplace. The dishes were then returned for analysis. No significant correlation could be demonstrated. Cf., however the case histories 8 and 10.

The question which now arises is: do these positive skin reactions actually mean that the hypersensitivity to mould is of importance for the patient? In many cases it can be proved that a certain allergy to mould hardly exists, in other cases it is very probable that the patient's disease arises wholly or partially from mould.

In some of these cases we made a passive transfer according to *Prausnitz* and *Küstner* and always reached positive results. Evidently in those cases there were humoral antibodies against the various types of mould. These experiments of transferring have been made only in a limited number of cases because of the obvious risk of serum hepatitis during such experiments.

The only sure proof of a certain allergy is through a positive provocation experiment.

For that experiment various methods may be used.

(1) *The Conjunctival Test*. This test, however, does not prove much more than the skin test since we have no guarantee that there is a larger correlation between the conjunctivitis and the respiration tubes than between the skin and the respiration tubes.

(2) *The Nasal Test*. This method is hard to judge because of unspecific reactions.

(3) *The Bronchial Test*. In this test the patient inhales the allergen. This method is closest to the natural exposure.

In the literature there are few descriptions of the way in which the authors have tried to separate the real mould allergies by provocation experiments. *Harris* arranged a mould room, where he kept a certain number of mould spores (*Alternaria*) circulating by fans and where the patient stayed for one hour. Of 12 patients suspected according to the anamnesis 8 developed the symptoms of asthma after 10-60 minutes. Out of 10 patients who had reacted to *Alternaria* but where it was not according to the anamnesis probable that *Alternaria* redeemed their asthma only one patient showed any symptoms of asthma. *Penington* tested 526 patients with 52 different mould-extracts and received positive skin reactions in 85 per cent of the cases. 67 were suspect according to the anamnesis, and of these 22 reacted positively to sniffing spores or dripping extract 1:20 into one nostril. This gives about 4 per cent of clinically certified mould allergy. 43 or 7.3 per cent showed reactions at the desensitizing, which probably means that a real mould allergy existed in these cases. *Blumstein* examined 406 patients with asthma, 41 per cent reacting positively to the mould extract. At the nasal tests positive reactions were reached only in 12 cases or 3 per cent. All the patients with positive provocation experiments were in the group of seasonal asthma. In the group of perennial asthma there were 158 patients, of whom 51 had positive skin reactions, but no one gave positive provocation experiments. *Reymann* and *Schwartz* have made conjunctival tests with extract 1:100 on 6 patients, who reacted positively to the intracutaneous test with mould from their own home-dust, but in no case a positive reaction was obtained from the conjunctival test.

Evidently there is a significant discrepancy between positive skin reactions and positive provocation experiments with mould. The following explanations may be possible.

(1) There is quite a low percentage of real mould allergy. The majority of the positive skin reactions represent latent allergy or a non-specific irritation.

(2) The provocation methods are not reliable.

We have made provocation experiments on most of the 23 mould-positive patients, who are in the asthma bronchiale group. The nasal test has been made either by the patient's sniffing spores in one nostril or by using a couple of drops of the extract in the concentration 1 : 20. The bronchial test has also been used. To begin with a hand spray was used (Leo's pocket inhaler) and the patient inhaled 0.5 ml extract 1 : 20 for 10 minutes. After a while the technique was changed so that the patient was given the extract through a spray constructed by *Barach* instead, a spray in which the extract is nebulized by supplying oxygen gas from an oxygen gas bomb. As a criterion of positive reaction it has been proposed that the patient would show subjective symptoms of asthma and that it would be possible to register peep and rhonchi from the lungs.

No certain positive result of the provocation experiments was reached either with the nasal test or with the bronchial test.

The question then arose whether as a whole it is possible to provoke asthma in this manner. Therefore provocation experiments were made with some other allergens, dust, pollen, horsehair, cattle, etc., where it was very likely according to the anamnesis that the allergen under consideration was the cause of the patient's asthma. The attempt to get any positive provocation experiment with dust asthma was unsuccessful. In two cases positive results were reached with pollen allergy and in one case with sensitivity to horsehair a positive result was also obtained. In all the other cases (about 100) where in all probability the allergen could be traced according to the patient's own statements, the provocation experiments were negative.

As a matter of fact it seems as if only on rare occasions

it should be possible experimentally to reproduce asthma bronchiale with up to date methods.

Therefore we have been unable to reach further than to a probability diagnosis, that the mould spores have been completely or partly the cause of the patient's allergy. We have made this diagnosis on the anamnesis in the first place and have correlated the skin reactions with it. We have been confirmed in our supposition if the patient, during the desensitizing, has developed asthma, other allergic symptoms, or fever.

Our clinical patients were 123, for whom the main diagnosis was asthma bronchiale. In many cases the patients also suffered from hay fever. 23 of these patients or 18 per cent reacted positively to one or more types of moulds. If we apply the above-mentioned critical points of view, however, we have to separate out 11 cases, where it is not probable that the mould has had any influence on the patient's trouble. Hence there remain 12 cases (10 per cent) of the patients where it is probable that the mould has been of etiological importance. A short report of these cases is given in the case histories (cases 1-12).

The number of our polyclinical patients with various allergic reactions was 1250 and of these 127 (10 per cent) showed positive skin reactions to one or more types of mould. Of these there are only 52 cases, however, where the mould might completely or partially be of etiological importance. It is quite natural that the percentage becomes lower than with the clinical patients since many of the cases sent for testing at a closer investigation of the anamnesis prove to be illnesses of not surely allergic nature. It is found that mould as an allergen is important also in cases of allergic diseases other than asthma and hay fever. This is true for instance of some cases of conjunctivitis (17-19) and of skin diseases (20-21).

Dust and Mould Allergy.

Dust is the allergen to which the patient most frequently reacts. 49.5 per cent of our clinical patients with asthma bronchiale reacted positively to dust. There has been much speculation on the active ingredient in the dust. Also mould has been mentioned. Already *Storm van Leeuwen* mentioned the role played by mould and his opinion was that *Aspergillus*, which he isolated from dust of an asthma patient's mattress was the active factor in the dust. *Rackemann* and *Wagner* showed that allergenic substances were created in formerly inactive kapok under the influence of mould.

Several researchers, *Cohen et al.*, *Brown*; *Rackemann* and *Schwartz* have cultivated mould from different types of house dust. The patient has then been tested both with his house dust and with the types of mould cultivated, but none of these authors has been able to prove any correlation between the house dust and the mould allergy.

In our case most patients react to dust but not to mould. Thus 49.5 per cent were sensitive to dust but only 10 per cent to mould. Evidently the mould as such may not have been the active substance of the dust, but it must be stated that under the influence of mould active allergens can develop in the dust.

If we examine the patients who have reacted to mould (Table 7) we find, of course, that in most cases they have also showed reaction to dust. There is, however, a large group of patients who have not at the same time reacted to dust, namely those who have reacted only to mould, and those who have reacted to mould and other inhalants except dust, —in all 24 per cent. Therefore *Feinberg's* statement, that patients allergic to mould almost always are allergic to dust also, does not stand the test.

Are the Allergic Reactions to Mould Specific to Genus or Species?

Feinberg says that we must count only on specificity to

genus. *Pratt* has made experiments with the *Alternaria* and obtained the same result. Opposite opinions have been stated as well. *Rackemann* says that we must count on specificity to species, an opinion shared by Danish researchers. *Flensburg* and *Barfod* tested various species of *Aspergillus* and *Penicillium* and did not find any agreement in the skin reactions to different species within the same genus. *Reymann* and *Schwartz* had the same experience in examining different species of the *Penicillium* genus.

To get some experience ourselves in this matter 9 different species of *Penicillium* were isolated. They were obtained from plates exposed in asthma patient's homes. Extracts were made from the different sorts and some patients were tested.

As shown in Table 8 we have been unable to prove any connection between different species of mould within the same genus. This leads to very complicated consequences because the genus *Penicillium* has several hundred species and the genus *Aspergillus* about fifty. Also in other mould genera there are generally different species, though not so many. If the mould allergy is specific to species there is no point in making an ordinary routine test with mould extract, which may only contain one or a few species of each genus. In order to completely investigate a patient's mould allergy the only possible way would be to make an analysis of his mould milieu by exposing plates in his home, in the workplace, etc. Then an extract should be made of every species of mould found and finally the patient should be tested with these specially made extracts. This, of course, is a very laborious and slow method, but in this way it may be possible to obtain better results than by the usual routine test.

CASE HISTORIES

Asthma bronchiale (in many cases also allergic rhinitis)

The patients treated in the Medical Department 1947 or 1948.

Case 1. B. L. ♂ 20 yrs. Diagnosis: Asthma bronchiale.

The father suffers from asthma. The parents have a bakery. The patient helped in the bakery. A couple of years ago he developed a bad cough and shortness of breath. This condition was particularly acute during the afternoon. He quitted the work in the bakery and was well until the autumn of 1947. At this time he did farm work and was again troubled with the above symptoms, particularly when in the barn or helping with the treshing. The patient's ordinary job is as an office clerk and when he is working in the city he has no trouble whatsoever.

Tests: *Hormodendrum*: + + +, *Penicillium IV*: + +.

Was desensitized to mould.

According to the anamnesis highly suspected of a mould allergy. The positive skin reactions to mould confirms the supposition.

The patient is still under treatment. Has no asthma.

Case 2. B. N. ♀ 24 years. Diagnosis Urticaria + Rhinitis allergica.

The grandmother suffered from asthma. At the age of 7-8 years the patient noticed that she developed eruptions on the skin from eating strawberries. Sometimes also ache in the left ankle. Trouble passes quickly. Also noticed being sensitive to mould. Only had to open a jar of jam with mould on top to get irritation and at the same time watery secretion in the nose. Cannot go into a barn without getting out of breath and getting hay fever.

Tests: *Penicillium*: + +, *Mucor*: + +.

Was desensitized to mould.

The patient herself has noticed that she is sensitive to mould. Above all the mould in jars of jam. Her reaction to Penicillium and Mucor at the tests agrees, since these are typical indoor types of mould.

The patient says that she has now after the treatment been completely free from trouble for 6 months. Can even smell mould without developing trouble.

Case 3. A. E. ♀ 20 years. Diagnosis: Asthma bronchiale.

The patient's asthma started at 8. In 1937 the pat. was tested and desensitized to dust, horse, and hay. After that all right. During stay in England 1947 she lived in a damp and mouldy apartment and began to develop asthma.

Tests: *Dust*: + + +, *Hormodendrum*: + + +, *Penicillium*: +, *Pullularia*: + + +, *Torula*: + + +, *Aspergillus*: + + + +, *Botrytis*: + + + +, *Horse*: + + +, *Cattle*: + +, *Pollen*: + +.

Was desensitized to dust, mould, pollen.

Patient has a previously diagnosed dust asthma. Made free from that by desensitizing. Besides there is a mould allergy which makes the patient's asthma break out when she is exposed to plenty of mould.

The patient has no asthma after desensitizing a little more than a year ago.

Case 4. A. N. ♀ 20 years. Diagnosis: Asthma bronchiale.

Uncle has asthma. Besides that no allergy hereditarily. The pat.'s asthma

started when she was one year old. Since then troubled yearly. In Örebro hospital for the first time 1945 in status asthmaticus. At the tests with standard extracts (no mould extract) the pat. reacted to dust and rye and was desensitized to these. The first year better, then trouble again. Became worse in connection with infection in the upper bronchiae. Better in Karlskoga city, where the patient has a modern apartment, than in the country. Has noticed that she is getting worse when the rye is blooming. Again hospitalized in 1946. New tests showed that the pat. also reacted to pollen besides to the above-mentioned extracts.

Was therefore desensitized. New trouble in March 1947.

New tests which also included mould extracts resulted in *Hormodendrum*: + + +, *Penicillium*: + + +, *Aspergillus*: + + +.

Provocation experiments (both sniffing spores and inhalation by spray of concentrated extract) were negative to all three mould types.

Passive transferring gave a strong positive result to as well *Hormodendrum* and *Penicillium*, as *Aspergillus*.

After a few days' stay in hospital the pat. was completely free from trouble. We started desensitizing with extract from *Hormodendrum*, *Penicillium*, and *Aspergillus* and started with a concentration of 1/10,000 mill. At the injection of 0.8 ml. 1/100, the pat. developed severe asthma which gave way after 6 hrs. Then the concentration of the extract was lowered to increase again. Fresh asthma attack after injection of 0.8 ml. 1/10. After about a day we started 0.1 ml. 1/10, but already after the following injection asthma started again; hence desensitizing was not carried on. Will continue the desensitizing with 0.5 ml. 1/100 per month.

The patient showed strong skin reactions to mould. Provocation experiments neg. However, she does have antibodies against those mould species, as is shown at the experiments with passive transferring. She also develops severe asthma symptoms at injection of more concentrated extracts while desensitizing.

Case 5. O. H. ♂ 60 years. Diagnosis: Asthma bronchiale.

A daughter has eczema. A niece develops skin-eruptions from strawberries. The pat.'s asthma started at 25. Has noticed that his trouble is caused indoors by dust and outdoors by fog. Cannot at all take part in threshing or harvest. Has noticed himself that he gets a sort of influenza from pollen of timothy grass and rye and also from mould.

Tests: *Dust*: + +, *Penicillium*: + + +, *Mucor*: + +, *Horse*: + +, *Cattle*: + + +, *Rye*: + +, *Barley*: + +.

The pat. was desensitized to these allergens.

According to anamnesis one suspects dust and mould allergy and skin reactions confirm the supposition.

Case 6. K.-O. E. ♂ 21 years. Diagnosis: Asthma bronchiale.

The mother, the grandfather, and four male cousins suffer from asthma.

The pat.'s asthma started at 2. Worst in the spring and early summer. At any season when entering a barn. Worse in foggy weather.

Tests: *Dust*: + + +, *Hormodendrum*: +, *Penicillium*: + +, *Mucor*: + +, *Botrytis*: +, *Cat*: + + +, *Horse*: + + + +.

Pat. was desensitized. He got asthma and a wide-spread urticaria at the injection of concentrated extract.

Strong allergy to horse and cat's hair. Also seasonal troubles worst in spring and early summer, without any pollen allergy these probably being due to the pat.'s mould allergy. The pat. shows strong reactions at desensitizing, but whether they are to be classified as mould allergy or hypersensitivity to horse and cat cannot be settled.

Case 7. A. J. ♀ 63 years. Diagnosis: Asthma bronchiale + Rhinitis allergica.

Hay fever started in 1944, asthma since 1945. Trouble above all during the summer. Midsummer Eve 1945 the pat. spent in the country and was struck by a bad attack of asthma during the night. Thereafter asthma trouble all the summer. In Sept. 1945 the pat. was taken to the hospital of Söderhamn and became well immediately. During the late summer and autumn of 1946 trouble again, also during the same season in 1947.

Tests: *Hormodendrum*: +, *Penicillium*: +, *Botrytis*: +, *Hay*: +, *Straw*: +.

Pat. was desensitized.

Considering that the pat. had trouble exactly during the mould season every year and that she showed reactions to mould, it is probable that her case is a mould allergy.

Six months after leaving hospital the pat. was practically free from trouble. Insignificant trouble just during the mould season. Gets local infiltration at the place of injection after the squirt of extracts, which the pat. receives once a month.

Case 8. E. P. ♀ 45 years. Diagnosis: Bronchitis asthmatica.

3-4 months before hospitalization the pat. came down with a tickling cough without any preceding cold and with difficulty in breathing. Especially bad during the night. Better when she is outdoors. No fever.

Tests: *Dust*: + + +, *Mucor*: + + +, *Botrytis*: + + +.

Petri dishes exposed in her home: Overgrown with *Mucor*.

Desensitized.

A short anamnesis but the fact that the pat. has trouble indoors, that she reacts strongly to Mucor at the test and that there are Mucor spores in her home, all makes it probable that the pat. has a mould allergy.

At an examination 9 months later the patient told that she had been completely free from trouble since the stay in the hospital.

Case 9. S. B. ♀ 41 years. Diagnosis: Asthma bronchiale + Rhinitis allergica. Mother, brother, and aunt suffering from hay fever. The pat. herself has

had urticaria from time to time. Asthma since 1933, hay fever since 1937. Trouble the whole year, worst in July.

Tests: *Dust*: +, *Hormodendrum*: ++, *Mucor*: +, *Botrytis*: ++, *Pollen*: ++.

Desensitized. To begin with free from trouble, at the end of desensitizing asthmatic troubles.

Probably a dust asthma combined with pollen and mould allergy. The fact that the patient is worst in July agrees well with mould allergy. Besides, the pat. developed asthma at the desensitizing, which also confirms the supposition that she is hypersensitive to the allergens mentioned.

At an examination 10 months after dehospitalization the pat. told that she had been completely free from asthma, even during July.

Case 10. N. B. ♀ 69 years. Diagnosis Asthma bronchiale + Rhinitis allergica.

... Since the autumn of 1946 she has had attacks of rhinitis especially in foggy and stormy weather. Sometimes without any reason when she went to bed. From time to time also a bad cough and difficulty in breathing, had to sit up several nights to breathe. No fever. Viscous expectoration. When pat. was hospitalized she was free from trouble without any further treatment.

Tests: *Dust*: +++, *Hormodendrum*: +, *Botrytis*: +.

Petri dishes in the home: Plenty of *Hormodendrum*, some *Penicillium* and a little *Mucor*. Was desensitized.

The correlation between the trouble at night at home, the positive skin reaction to Hormodendrum, and the frequency of Hormodendrum in the home make one suspect that a mould allergy is at least a contributory etiological cause.

Case 11. E. B. ♀ 54 years. Diagnosis: Asthma bronchiale + Rhinitis allergica.

Hay fever and asthma since 1941. Trouble above all in summer. Better when she is staying in the city than in the country. Change for the worse when in barn. Very bad when taking part in treshing.

Tests: *Hay*: ++, *Pollen*: ++, *Hormodendrum*: ++.

Desensitized. When reaching concentrated extracts a slight fever arose, wheeze in the chest and difficulty in breathing. Local reaction at the place of injection. The concentration was lowered and injections were started again, but at larger quantities again rather bad asthma and increased temperature.

The anamnesis agrees well with a pollen and mould allergy. That these allergens are important also appears from the fact that the pat. has trouble at desensitizing.

Pat. says she is now better but still has some trouble.

Case 12. K. B. ♀ 38 years. Diagnosis: Asthma bronchiale + Rhinitis allergica.

Hay fever and asthma started in 1944. Trouble only from May to the summer. Well in the winter. The trouble may last several consecutive weeks.

Tests: *Dust*: ++, *Hormodendrum*: ++, *Pollen*: ++.

Was desensitized.

Considering the seasonal troubles and the fact that the season exceeds the grass pollen season it is probable that it is a combined pollen and mould allergy.

The patient at an after examination claims that she is not better.

Some typical cases of polyclinical patients.

Allergic rhinitis.

Case 13. I. B. ♀ 15 years. For many years hay fever. Worst in the autumn. Last autumn very bad. May have noticed that dust has been a contributing factor, but besides that no notice of any cause of her hay fever.

Tests: *Dust*: ++, *Botrytis*: ++, *Hormodendrum*: ++, *Penicillium*: ++, *Woodflour*: ++.

It is probably a combined dust and mould rhinitis. The pat. has trouble just during the mould season, but is fairly well during the rest of the year.

Case 14. G. K. ♂ 28 years. For a couple of years periods of hay fever. Worst in summertime. Much better in the winter. Has not noticed any cause.

Tests: *Dust*: ++, *Botrytis*: ++, *Hormodendrum*: ++.

Also in this case one must suspect a combined dust and mould rhinitis since the patient has trouble during the mould season and is well during rest of the year.

Case 15. E. E. ♂ 30 years. As a boy the pat. was employed in a grocery and when he dusted the floor he got nose secretion. The pat. has recently opened his own shop, and the secretion starts when he handles hip flour or sugar dust.

Tests: *Botrytis*: ++, *Penicillium*: ++, *Dust*: +.

Spore analysis has shown that in a grocer's shop and such places there is plenty of mould especially Penicillium. Therefore it is very probable that the pat.'s secretion is caused by mould.

Case 16. J. J. ♀ 48 years. From the age of three trouble with hay fever, lack of air and difficulty in breathing as from asthma. It starts in the early summer, gets worse during Sept. and Oct. Better in winter. Worse in dusty and foggy and damp air.

Tests: *Dust*: +++, *Hormodendrum*: ++, *Penicillium*: ++, *Horse*: ++.

Considering that the pat.'s troubles are correlated with the mould season it is probable that her hypersensitivity to mould is at least contributory to her trouble.

Conjunctivitis.

Case 17. T. S. ♀ 42 years. In the autumn a year ago very bad eye catarrh. This autumn again the same trouble. Has not had a cold.

Tests: *Hormodendrum*: ++.

The fact that the patient's trouble comes when the spore content of *Hormodendrum* in the air is at its highest and her hypersensitivity to this type of mould, bring about, that we must consider it probable that her trouble is a mould allergy.

Case 18. A. M. ♀ 36 years. During the summer 1947 the patient began to get catarrh in the eyelids with frequent conjunctivitis. Has not had a cold. Continued the whole autumn.

Tests: Dust: ++, *Hormodendrum*: ++, *Botrytis*: ++, *Penicillium*: ++. Timothy grass pollen: ++.

Since the pat. has trouble both during the pollen season and during the mould season it is probable that it is a case of combined pollen and mould allergy.

Case 19. G. L. ♀ 13 years. During the whole autumn has had a stubborn conjunctivitis. Has not had a cold.

Tests: *Hormodendrum*: ++, *Botrytis*: ++.

The same discussion as in case 17.

Skin diseases.

Case 20. V. K. ♀ 46 years. For several weeks trouble with eczema on the face. It started around the eyes and spread all over the face. Started in connection with the pat.'s taking part in treshing. After that she has noticed herself that she has become worse when coming into contact with husks and hay.

Tests: *Hormodendrum*: ++, Straw: ++.

The extremely rich mould content in the air at threshing as well as in hay and straw proves that it cannot be denied that mould has contributed to the pat.'s trouble, since she proves to be hypersensitive to mould at the skin test.

Case 21. K. Z. ♂ 23 years. Garden worker. For a year eczema on both hands. It started in connection with weeding at hotbed. Getting worse every time he works in the green houses.

Tests: *Mucor*: +, *Penicillium*: ++.

In connection with the investigation of the milieu it was stated that there are a great many mould spores in the air of a green house and also in the earth. Therefore it is possible that the pat.'s eczema is due to an hypersensitivity to mould.

SUMMARY.

1. The mould spore content of the air in Örebro has been studied by daily observations for 18 months. Thereby pronounced seasonal variations with a mould season during the months June-October have been found. The most common spores originate from *Hormodendrum*, *Penicillium*, *Pullularia*, and *Yeast-like fungi*. With strong wind or fog the spore content will increase.
2. The spore content indoors has been analysed in a great number of homes. In homes with bad hygienic conditions the spore content has been higher than in better homes. The commonest type of mould indoors is *Penicillium*. Also *Aspergillus* and *Mucor* occur indoors much more frequently than outdoors.
3. The spore content in different working-places varies significantly. In barns, greenhouses, vegetable factories, and groceries we often find a very high spore content.
4. Comparing the spore content in an average size city and in the surrounding country no difference was found.
5. In two large cities there were fewer spores, particularly *Hormodendrum*, than in smaller towns and in the country.
6. At a comparison of the spore content in the city of Örebro and Åre, a tourist place in the mountains of Jämtland, a slightly shorter mould season was found in the mountains. During the mould season the spore content was about as high in the mountains as in level country. *Hormodendrum* was not so frequently found in the mountains, but *Penicillium* was rather common. On the mountain above the timber line a smaller spore content was generally found. On certain occasions, however, even at these levels high values could be observed.
7. The spore content at different heights has been registered by airplane. On the higher levels the spore content was low but the spores existed up to 1000 m. The extremely high spore content in clouds is remarkable.

8. Extracts at a concentration of 1:2000 have been made of *Hormodendrum*, *Penicillium*, *Mucor*, and *Botrytis* and have been used for intracutaneous tests.
9. Clinical patients with the main diagnosis of asthma bronchiale have been examined. The number of them was 123, of whom 23 or 18 per cent reacted positively to one or more mould types.
10. Polyclinic patients with mixed allergic and suspected allergic symptoms have also been investigated. Of 1250 cases, 127 (10 per cent) reacted positively to mould.
11. More detailed investigations have been made to determine the role the mould allergy has played in giving rise to the trouble in each separate case. Passive transfer according to *Prausnitz-Küstner* has been made in some cases,—in all of them with positive results. Provocation experiments according to the bronchial test method have been made in most cases of asthma bronchiale, although with negative results.
12. The probability diagnosis: clinical mould allergy therefore has been set on the anamnesis correlated with the skin reactions. In some cases the diagnosis has been confirmed by the patient's developing asthma, urticaria, or fever at the desensitizing.
13. The probability diagnosis: clinical mould allergy has been found in 12 cases or 10 per cent of the clinical patients sorted out in this way. Among the polyclinic patients 52 such cases or 4 per cent were found.
14. Besides being important to the allergic diseases in the respiration tubes hay fever and asthma, the mould allergy may be important to the origin of conjunctivitis and skin diseases.
15. No correlation between dust and mould allergy has been demonstrated.
16. It is shown for *Penicillium* that from the point of view of hypersensitivity there is a specificity to species and not to genus. This fact makes the test by standard extracts unreliable. Therefore it is necessary to make an

analysis in each single case of the patient's home milieu and then to make extracts of the specific types of mould and test the pat. with them. For other mould genera the same is probably true.

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BOOK REVIEW

Medical Survey of Tristan da Cunha. By Sverre Dick Henriksen and Per Oeding, Norway. Pp. 147, with 42 illustrations. Published by Det Norske Videnskaps-Akademi. On commission to: Jacob Dybwad, Oslo, 1940. Price: 8.— kroner (Norwegian).

This report is part of a very interesting work published under the title: *Results of the Norwegian Scientific Expedition to Tristan da Cunha 1937-1938.* It presents a compilation of thoroughly performed medical investigations and although the conditions of life on the island may have been altered in the after-war-time the Norwegian results render important contribution to several fields in medical research. Particularly it is of interest to allergists on account of the surprising fact, that allergic diseases were the most common group of diseases found on this little island in the South Atlantic Ocean.

The conditions of human life on Tristan da Cunha were found to be very meagre, because it lacks almost everything, which helps a population to be selfsupporting. The life is monotonous, the diet very simple, composed of a few different articles of food: potatoes, fish, meat, seabirds and eggs in a quantity, which yields only a moderate amount of energy.

Besides mild cases of common cold, dysentery, widespread infection with *ascaris lumbricoides* and slight hereditary deformities, the only group of diseases with rather high frequency was that of allergic disorders.

Among the 188 individuals living on the island the authors found 29 persons suffering from typical allergic diseases, while 27 others were suspicious of allergy, a percentage of between 15.4 and 30. Most frequent was asthma, 19 persons either gave a typical history of asthma or had attacks during the stay of the expedition and 23 could tell about attacks of tightness on the chest, which may or may not have been asthmatic. Four persons suffered from hay fever, elicited by a common grass on Tristan da Cunha (*holcus lanatus*). Six women suffered from a typical migraine and six other from headache of a less characteristic type. Two persons had chronic eczema and one woman gave a history of food allergy. Moreover the authors found one case of conjunctivitis aestivalis and six cases of nasal polyps, probably due to allergic rhinitis.

It is a matter of uttermost interest that the expedition obtained convincing information, that three of the original settlers had suffered from asthma and

that nearly all allergic individuals on the island belonged to their families. Of course the figures must be too small for definite conclusions. However, in studying the two pedigress presented by the authors we gain support of the theory that hereditary factors play an important role in the pathogenesis of allergic diseases and that the mode of inheritance is as a Mendelian dominant. The pedigrees speak against the view about the inheritance of the shock organ, because asthma, hay fever and migraine occurred without definite rule in the same family.

This frequency of allergic disorders had not been expected by the expedition in advance; therefore, no cutaneous tests were carried out.

Besides the allergic investigations the report contains several important results, the most interesting of which is the fact, that even though the life on Tristan da Cunha was much different from what would be considered ideal by modern hygiene, it seemed to be good for the health, the only group of diseases of any importance being one, which is based upon hereditary disposition.

The purpose of this brief review is to call allergists' attention to an important, scientific medical work, which according to the modesty of the Norwegians has been hidden among botanical, zoological and geological reports.

Poul H. Nexmand,
Copenhagen.

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MIGRAINE AND ALLERGY¹

By

GUNNAR HACKZELL, M.D., SVEN KRAEPELIEN, M.D., and
BO VAHLQUIST, M.D.

During the past few decades, it has been asserted in a large number of investigations, particularly in the United States, that migraine should be regarded as an allergic disease (Vaughan, 1927; survey by Vaughan and Black, 1948). This view is based on the following observations: (1) occurrence of allergic manifestations in the migraine patients themselves, as well as in their relatives; (2) according to the sick history appearance of attacks after the ingestion of certain foods; (3) positive skin tests indicating specific hypersensitiveness; (4) positive results of exposure to specific allergens; (5) good therapeutic results with desensitization and/or elimination diet.

Since the autumn of 1947, we have been analysing the allergic picture in some of the approximately 250 cases of migraine we have had under observation in connection with studies of the migraine syndrome in different ages (Vahlquist et al., 1949).

Material: 40 cases of migraine have been examined, 25 of them women and 15 men. The youngest patient was five years old and the oldest 49. The age group, 5 to 14 years, comprised 15 patients. All the cases presented a typical picture of migraine. In addition to paroxysmal headache, they had at least two and often three or four of the following characteristics: typical heredity, nausea, flimmer scotoma and hemicrania. In selecting our material, we gave priority to patients who had relatively frequent and severe attacks,

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and we also favoured patients who lived near enough to the hospital to be able conveniently to report for examinations.

Method: A detailed history was taken down of all the cases, with special attention to allergic manifestations in the patients themselves and also in their parents and siblings. All the patients were submitted to skin testing by the intracutaneous method. Tests were made with forty of the nutrition and inhalation allergens commonly met with in Sweden.

The inhalation allergens included dust and pollen extracts, extracts of feathers, straw, hay, lycopod, mould, wool, cattle and horse, cat and dog hair. The nutritive allergens included chocolate, fish and meat of various kinds, lobster, yeast, cereals, milk, egg, and different kinds of vegetables. The reaction was read about twenty minutes after the injection of the allergen, and the positive results were evaluated in relation to the histamine weal used as a control.

Experiments with exposure were made in a few cases, in which the history or the skin test had given us reason to suspect the presence of allergy.

In 14 cases the patients were treated with Antasten,¹ an antihistamine preparation. Here priority was given to persons who had given positive reactions to the intradermal tests.

Results: In order to facilitate evaluation of the results, we have collected a material for comparison, which consists of a series of 40 asthmatic children treated at the Norrtull Hospital in the year 1947 and of a normal series comprising 80 adults, all of them employed at the hospital.

Allergic diseases in parents and siblings are presented in Table 1, from which it appears that the incidence of positive allergic heredity in the present material does not differ substantially from that in the normal material. There is an appreciable numerical difference in the incidence of eczema as compared with the asthma material. The total incidence of allergic manifestations is 14 per cent in the migraine group and 33 per cent in the asthmatic group. The difference, 19 ± 5.1 per cent, is statistically significant. However, it should be borne in mind that the data in the asthma group were provided by the mother and undoubtedly are more complete than in the migraine group, in which the

¹ We are indebted to AB *Ciba-Produkt* for their kindness in supplying us with *Antasten* (*Antistin*).

TABLE 1

The incidence of allergic diseases in close relatives of patients with migraine and asthma as compared with normal subjects.

	Total no. of parents and siblings	In parents and siblings				
		Asthma	Eczema	Urtica- ria	Hay- fever	Other allergy
Migraine material (38 cases)	156	4 %	4 %	5 %	0	1 %
Asthma material (40 cases)	117	6 %	13 %	6 %	6 %	2 %
Normal material (80 cases)	371	3 %	3 %	4 %	2 %	1 %

patients themselves usually supplied the information. In view of this, the differences are remarkably small between the migraine and the normal material on the one hand and the asthma material on the other.

With regard to the presence of allergic diseases in the patients themselves, the figures are about the same for the migraine and the normal material, as appears in Table 2. The asthmatic children show considerably higher rates for eczema, urticaria, and "other" allergic diseases. In this case, too, it must be assumed that the data for the asthmatic patients are more complete than for the other groups, since the mothers obviously had clearer memories of the illnesses of early childhood than the patients themselves.

The unreliability of second-hand information appears

TABLE 2

The incidence of allergic diseases in patients with migraine and asthma as compared with normal subjects.

	Number exami- ned	Asthma	Eczema	Urtica- ria	Hay- fever	Other allergy
Migraine material	39	8 %	21 %	23 %	5 %	8 %
Asthma material	40	—	60 %	25 %	0	18 %
Normal material	88	5 %	23 %	24 %	5 %	5 %

from the great difference in the incidence of allergic diseases in the normal persons themselves on the one hand (Table 2) and in their relatives on the other (Table 1).

Table 3 lists the factors that, according to the migraine patients themselves, provoked the attacks. It appears that allergy was suspected to be the inciting factor in only a very small number of cases, and that psychic factors dominated.

TABLE 3

Factors precipitating the attacks of migraine as elicited from the sick histories of the patients.

Number examined	Factors reported to bring on migraine				
	Allergy ¹⁾	Psychic factors ²⁾	Physical factors ³⁾	Menstruation ⁴⁾	Unknown
39	8 %	59 %	36 %	(29 %)	15 %

¹ Various foods.

² Tension, worry, late nights, etc.

³ Physical exertion, hunger, light, cold, etc.

⁴ 5 of 20 women over 15 years.

The allergen tests gave completely negative results in not less than 27 of 40 cases. However, 13 of the migraine patients tested showed positive skin reactions of varying strength to different allergens. The results are shown in Table 4. It appears from this table that the inhalation allergens dominated, while the nutrition allergens were only scantily represented with, oddly enough, not a single positive cutaneous reaction to vegetables. Three of the 13 patients with positive skin reactions had asthma, combined with *febris aestivalis* in one case and with urticaria and eczema in another. Two of the patients had eczema only and four gave a history of urticaria.

A comparison between the incidence and strength of the positive skin reactions in the present migraine material and the asthma material appears from Table 5. A distinct discrepancy will be noted.

TABLE 4
The types of allergies observed in 13 patients with migraine. A further 27 patients failed to give any positive intradermal reactions.

	Household dust	Matress dust	Timothy pollen	Birch pollen	Cattle hair	Horse hair	Wool	Hazelnut	Lobster	Raw egg yolk	Boiled milk	Feathers	Allergic complaints
Case 4. K. A.	++	++	++	++			++						Urticaria ¹
" 5. L. A.	++		++	++			++			+		+	Eczema
" 9. I. C.	++	++	++	++	++	++	++	+	++	++			Urticaria
" 13. M. H.	++	++	++	++	++	++	++						Asthma, urticaria and eczema
" 16. G. J.	++		++				++						Urticaria
" 18. S. J.	+	++	++	++	++	++	++		++				Urticaria
" 24. S. N.	++	++	++	++	++	++	++		++				Eczema
" 26. G. P.	++		++	++	++	++	++		++				— ²
" 28. I. R.	++		++	++	++	++	++		++				— ³
" 29. J. R.	++	++	++	++	++	++	++	+			++	+	Asthma ³
" 33. T. S.	++	++	++	++	++	++	++	++			++	++	— ⁴
" 34. A. T.	++	+	++	++	++	++	++	++	++				Asthma and Febris aestivalis.
" 37. B. W.	++	++	++	++	++	++	++	++	++				

¹ Slightly positive reactions to hay and raw egg white also.

² Slightly positive reaction to uncooked milk only.

³ Slightly positive reactions to fish, straw, uncooked milk, and mould also.

⁴ Slightly positive reaction to barley also.

TABLE 5

The intensity of the skin reactions in a material of patients with migraine as compared with asthma patients.

Strength of intracutaneous reactions	Migraine material (40 cases)	Asthma material (40 cases)
+	21	47
++	18	75
+++		
++++	19	117
+++++		

As appears from Table 3, intake of certain foods was suspected as the cause of the migraine attacks in only three cases. Exposure experiments in the same three cases, the only ones to be made, were completely negative.

Treatment with *Antasten* tablets was tried in 14 cases. The preparation was given in doses corresponding to 4 to 5 mg. per kilogram body weight over a period of about one month. Seven cases suffered definite side-effects in the form of tiredness, nausea, and giddiness, which were severe enough in some instances to necessitate reduction of the dose. Two of the patients who had attacks of migraine on an average of two to four times a month reported a considerable improvement, which lasted for two or three months after cessation of the treatment. Four patients stated that there was some improvement during the course of the treatment, and the remaining eight observed no effect of the preparation whatever. In view of the well-known suggestibility of migraine patients, care must be taken not to overestimate the importance of occasional positive results. Similar results have previously been obtained by Kallós (1947).

DISCUSSION

The preceding results differ considerably from those observed by certain American allergologists. And even fewer positive findings were recorded than in the study of a Swedish

material recently published by Bergqvist (1948). What is the explanation?

Certain observations would suggest that the incidence of allergic diseases actually is greater in the United States than in Sweden. But this would scarcely account for a disproportionately high rate of allergic migraine. It is difficult to compare the total incidence of typical migraine in the two countries. A thorough analysis of the real incidence of migraine in Sweden has been conducted by Vahlquist et al. (1949). Certain investigations suggest that the mean incidence may be much the same in the United States (Balyeat and Rinkel, 1931, Grimes 1931).

In the present discussion, it is obviously of fundamental importance that the criteria for allergy be approximately uniform. We shall confine ourselves in this connection to the skin tests.

The extracts used in our tests (manufactured by the *Vitrum* company in Stockholm) presumably are not inferior to foreign products. They have been submitted to a series of thorough comparative clinical tests, and have yielded corresponding results in the hands of different investigators.

It is impossible to say how far differences in evaluation of the reactions obtained are to be blamed for discrepancies in the results. As appears from the description of the method, our reactions were always evaluated in relation to a standard histamine weal.

The number and the type of test extracts varies with different investigators. But even a comparison of the number of positive reactions with one and the same type of extract shows striking differences between the results obtained by American allergologists and those cited in the present study. The nutritional allergies predominate in the American reports, reaching as high as 100 per cent. In our series, on the other hand, the majority of positive reactions were due to inhalation allergens.

It cannot be denied that psychic factors play an important part in precipitating attacks of migraine. Proponents of the

allergic theory do not deny this, but claim that the psychic shock gives rise to a change in intestinal tone and peristalsis, which favours absorption of substances to which the patient is allergic. This line of reasoning seems to have little factual background. We have not been able to discover any roentgenological observations of stasis or antiperistalsis *before* an attack of migraine, whether spontaneous or provoked. That such changes may occur *during* the attack when the nausea has already developed is another matter; we have seen this happen ourselves in several cases.

Certain patients report that they regularly have attacks of migraine when they are under psychic strain, e.g. students after written examinations. It seems rather far-fetched to assume that the critical allergen or allergens are present in the intestine on all such occasions waiting to be absorbed just when absorption is going to be temporarily intensified.

Proof of the accuracy of the allergic theory in migraine is said to be found in the therapeutic results. Different allergologists report that between 50 and 80 per cent of patients treated by desensitization and/or elimination diet are cured or considerably improved (Eyermann, 1931; Balyeat, 1933; Hartsock and Mc Gurl 1938). These figures would be more convincing if other workers had not reported almost as good results with completely different treatments, which could not reasonably have had any effect on the allergic mechanisms. Grunert (1938), for example, stated that correction of refractive errors led to considerable improvement in 197 of 208 patients! Other workers report 60 to 70 per cent improved with histamine desensitization or with diet only (Goldzieher 1946). The endocrinologists have achieved excellent results with hormone treatment, and so on.

We do not doubt that in a certain number of cases, the attacks of migraine are really brought on invariably or on certain occasions by an allergic condition. But we believe that if good results are secured with an anti-allergic treatment in 60 to 80 per cent of a series, this is due in part to the cir-

cumstance that the material is a selected one from the point of view of allergy and in part to the well-known fact that migraine patients are suggestible, as well as susceptible to various measures which convince them that they have found an interested helper in their physician and that they must adhere to a specific regimen. Any kind of regimen is in itself an important form of psychotherapy to these individuals, who generally are very ambitious, but frequently inflexible and oppressed by a feeling of insecurity.

Our belief that the part played by allergy in precipitating attacks of migraine has been greatly over-estimated seems to correspond to that expressed by numerous well-known American physicians during the last few years. Wolff, for example, does not mention allergy or its treatment in "Management and prevention of migraine" in Cecil's Textbook (1947), and Palmer (1945) reported the elimination of allergy to be effective in at most 10 per cent of migraine cases.

As a conclusion to this paper, we should like to quote another prominent American physician, Dr. Alvarez of the Mayo Clinic (1947): "... the essential attribute of the typically migrainous person is his or her peculiar physical and mental and spiritual make up ... I always think of the migrainous storm in the brain as being like a mousetrap set off by a trigger. Allergy is just one of the things that can spring the trap."

SUMMARY

Forty persons with typical migraine were submitted to an allergy analysis. Skin tests gave positive results in 13 cases (Table 4 and 5). Seven of these showed multiple and in some cases strongly positive reactions; inhalation allergens were involved in the great majority of positive reactions. All seven patients had signs of allergic disease. The incidence of typical allergic diseases in the migraine patients themselves, as well as in their closest relatives, did not differ to any extent from

that in a control material (Tables 1 and 2). Treatment with a histamine antagonist (*Antasten*) had an appreciable effect in only 2 out of 14 cases.

The investigation does not support the theory that allergy is a common cause of migraine.

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PHYSIOTHERAPY OF ASTHMA RESPIRATORY EXERCISES

By

Dr. J. LÉVINTON and Kgo. ALBERTO CODON

Among the many treatments applied to the respiratory dysfunctions, and especially to asthma, physical measures and particularly respiratory exercises are outstanding today.

Most authors concur in the objective but they differ in the technique. Their object is to diminish the reserve air which the patient does not expel and to transform it into tidal air. This is obtained by means of the diaphragm. In order to get these results we applied the Kendall system to the abdominal muscles.

In order to eliminate any foreign particles (dust, pollens, etc.) we use a *Free Allergen Room* as a gymnasium. It has filtered and sterilized air with controlled humidity and temperature. Thus we avoid the danger of such particles irritating the delicate alveolar wall during deep inspirations, which are practically unavoidable. Some of these particles might act as irritants; others might be true allergens.

It is also necessary to teach the patient the nature of his disease and to explain to him the advantage of not breathing deeply, but that, on the contrary, he should expel as much air as possible. Having learnt this the patient can usually prevent or at least diminish the intensity of the attack. For this purpose we also teach the Short Diaphragmatic Breathing, with the patient lying on his right side, his thorax high, turned slightly on his face, and with his knees bent comfortably.

Having outlined these preliminary principles, we are going to describe briefly our plan or method of treatment.

A medical examination is first necessary to discard other factors which might contra-indicate the application of the physical treatment. Once we are sure his condition warrants it, the patient is taught the elementary principles of the respiratory exercises, that he must breathe exclusively with his

abdominal muscles so as to use the diaphragm to its fullest capacity, trying at the same time to relax the accessory breathing muscles (pectorals, sternocleidomastois, rhomboideus major, etc.). The inspiration must be short and the expiration long and slow.

The second time he is treated we apply sufficient exercises to create the so-called "first grade of suffocation of Lagrange", which is useful and stimulates the system. Exercises of the trunk and shoulders are also used. Sometimes it is necessary to reeducate the abdominal muscles, for which the Kendall System is the most suitable.

The thorax of this type of patient usually lacks elasticity. It is necessary, therefore, for the doctor to manipulate this region before each session. This lack of elasticity is observed in cases that have had a long development.

The exercises can be done in various positions, those most used being standing, sitting, and lying down. The principal exercises consist of flexions of the trunk accompanied by arm exercises, lateral flexions and rotations. All these must be done together with breathing exercises.

Rosenthal's principles must always be followed; the breathing must be rhythmic, nasal, silent, and with a physiological frequency of 16 to 18 respirations per minute. In the Short Diaphragmatic Breathing the frequency is from 25 to 40 respirations per minute.

If the nose or other passages are obstructed, the condition must be first corrected by a specialist surgeon.

In all cases we teach good posture, among other reasons because the patient usually presents himself tired, with drooping shoulders, downcast in manner and filled with lassitude. We use several methods, including equilibrium exercises which compel the patient to adopt a correct posture, and exercises for hyperextension of the trunk, directed towards the correct functioning of the anti-gravity muscle groups.

We commence with sessions of 10 minutes, slowly increasing them to 45 minutes, with intervals of rest between exercises to avoid fatigue.

Summarizing, we shall present a plan we have used with practical results, giving in detail some exercises of each type.

PLAN OF TREATMENT

Medical examination.

Somatic and kinetic function examination.

Physiotherapy treatment given simultaneously with the medical treatment).

In the first session the following things are taught:

A. Methods of avoiding onset of asthmatic attack:

1. Do not fight actively against the disease.
2. Do not breathe anxiously, since the problem does not consist in lack of air.
3. Learn methods of muscular relaxation.
4. Learn the Short Diaphragmatic Respiration when calm and not suffering an attack of asthma.

B. Abdominal respiration.

In the following sessions exercises are taught:

I. Tiring muscular exercises

- A. Shoulder girdle
- B. Trunk
- C. Abdominal (Kendall's technique).

II. Posture exercises

- A. Equilibrium
- B. Trunk hyperextension.

III. Passive movements of the thorax

IV. Respiratory exercises.

The length of the class was gradually increased from 10 to 45 minutes, and the number of the exercises from the minimum number given below to the maximum.

DESCRIPTION OF THE FUNDAMENTAL EXERCISES

I. *Tiring muscle exercises*

A. Shoulder-girdle

1. Elbow circling

Starting position—Seated, leaning forward with the back flat, fingers to shoulders, which should be kept well down, elbows in a straight line with shoulders. The back is held in the same forward leaning position throughout, to ensure that the movement takes place in the shoulder-girdle joints and not in the back.

Bring the elbows forward, down, back and up to shoulder position, making as complete a circle as possible.

Make 10 circles forward, then reverse direction and make 10 circles starting backwards.

2. Raising the shoulders

Starting position—standing or seated, arms hanging at the sides, feet together.

Raise and lower the shoulders, 8 to 15 times.

3. Raising the arms

Starting position—standing, arms hanging along the sides, feet separated.

Raise the arms forward to a vertical position and lower again to sides. 8 to 15 times.

B. Trunk

1. Flexion of the trunk

Starting position—standing, hands on hips, feet separated.

Bend forward slowly to a 90° angle, raise the chin as far as possible. Lower chin and return to upright position. 8 to 10 times.

2. Side-bending of the trunk

Starting position—standing, hands on hips, feet separated.

Bend the trunk from the waist sideways, without moving the head or bending the knees, alternating to right and left. 5 to 10 times to each side.

3. Trunk rotation

Starting position—standing, hands on hips, feet separated.

Rotate the trunk sideways to a 90° angle, moving the hips the least possible, alternating right and left. 5 to 10 times to each side.

C. Abdominal (Kendall's technique)

II. *Posturals*

A. Equilibrium

1. Knee bending

Starting position—standing, hands on hips, feet separated.

- a. Rise on tiptoes.
 - b. Lower body, bending the knees to about a 90° angle.
 - c. Raise the body upright.
 - d. Lower heels to starting position.
- 5 to 10 times.

2. Walking on tiptoe

Starting position—standing, hands on hips, feet together, a book balanced on the head.

- a. Rise on tiptoes.
 - b. Take ten steps forward on tiptoe.
 - c. Take ten short steps backwards on tiptoe.
 - d. Lower heels to starting position.
- 2 to 4 times.

3. Leg raising

Starting position—standing, hands on hips, feet together.

- a. Raise right leg to a horizontal position, lower to starting position.
 - b. Repeat same exercise with left leg.
- 10 times with each leg.

B. Trunk hyperextension

1. Simple hyperextension

Starting position—standing, or seated on a chair or bench, hands on hips, legs separated.

Bend trunk backwards as far as possible and return to upright position.

2. Hyperextension lying down

5 to 10 times.

Starting position—ventral decubitus, hands on hips, (after 10 sessions place hands on back of neck). An assistant holds the feet down.

Raise the trunk slowly to a 36° angle from horizontal position, then return to starting position.

3 to 10 times.

III. *Passive Movements of the Thorax*

The patient lies on his back on a cot with his arms along his sides. The physiotherapist stands at one side facing the patient.

The patient must relax all his muscles to the utmost. The physiotherapist places his hands along the lower edges of the thorax with the thumbs at the xiphoids, the thumbs being spread as far as possible from the fingers. He presses towards the patient's head and downwards, then reverses the movement and pulls upwards and towards the patient's feet.

IV. *Respiratory exercises*

1. Simple abdominal respiration

Starting position—dorsal decubitus, or reclining at a 30° angle, with pillows under shoulders and head, hands resting on the abdomen.

- a. Exhale slowly while gently lowering the chest as much as possible, and then the upper abdomen. When exhaling is finished, the abdomen should be well drawn in, the fingers resting either lightly on the upper part, or both hands should rest on the lower front margins of the ribs.
- b. Relax the upper abdomen so that it swells a little and the lower part of the chest is felt to expand slightly, while air is inhaled quickly but silently through the nose. The chest is not raised.

2. Complete abdominal respiration

Starting position—dorsal decubitus, arms crossed on the abdomen, knees raised and bent.

- a. Raise the trunk and head towards the knees, exhaling vigorously at the same time.
 - b. Return to starting position, inhaling slowly and silently.
- 3 to 10 times.

3. Flexion of the trunk

Starting position—seated, arms hanging along the sides, feet separated.

- a. Bend the head and trunk towards the knees, exhaling at the same time.
 - b. Return to starting position, inhaling gently.
- 3 to 10 times.

4. Side-bending with compression of the thorax

Starting position—seated, the right hand placed on the right lower thorax.

- a. Bend to the right, exhaling and pressing on the thorax with the right hand.

- b. Return to starting position, inhaling gently and with the hand relaxed.
5 to 10 times, alternating with the left hand and left side.

5. Trunk rotation

Starting position—standing, arms extended horizontally sideways, feet separated.

- a. Rotate the trunk to a 90° angle, exhaling at the same time.
- b. Return to starting position, inhaling gently.
10 to 20 times, alternating to left and right.

6. "Praying" exercise

Starting position—kneeling, arms raised over the head.

- a. Bend the trunk, bring the hands to the floor, exhaling.
- b. Return to starting position, inhaling gently.
5 to 10 times.

7. Short diaphragmatic breathing

Starting position—Lateral decubitus, either side will do, but generally the right side is preferable. Thorax should be high, supported with pillows; the arm on the under side reflexed; arm on top extended along side with a pillow under the armpit. The leg on the under side flexed; the leg on top extended.

- a. Exhale very sharply, contracting the abdominal muscles.
- b. Inhale rapidly but effortlessly, relaxing the abdomen.

25 to 40 respirations per minute. Increase time with practice from 1 to 5 minutes.

8. Teeter-totter exercise

Starting position—Dorsal decubitus on a "resuscitation table of Eye". Feet and shoulders are strapped to the table.

- a. An assistant lowers the head while the patient exhales and sharply contracts his abdominal muscles.
- b. The assistant raises the head while the patient inhales gently, relaxing the abdominal muscles.

15 to 20 respirations a minute. Increase time with practice from 3 to 5 minutes.

This is a very good exercise to use to avoid an attack of asthma, sometimes being more effective than the Short Diaphragmatic Breathing.

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INCIDENTS DE LA PÉNICILLINOTHÉRAPIE EN OTO-RHINO-LARYNGOLOGIE¹

Par

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Copenhague.

Déjà vers la fin de 1943, des auteurs américains (*Keefer et d'autres et Lyons*) ont rapporté divers incidents survenus après l'emploi de Pénicilline. On croyait d'abord qu'il s'agissait d'effets toxiques, cependant, les années suivantes, des communications ont parues tant de côté anglais (*Barker & Florey et Jennings*) que de l'Amérique (*Feinberg, Morris & Downing et Kolodny & Denhoff*) insistant sur l'atotoxicité de la Pénicilline. Selon ces auteurs, les effets notifs seraient dus à une hypersensibilité à la Pénicilline même ou à des impuretés dans les préparations. Or, au fur et à mesure que l'épuration des différentes préparations de Pénicilline s'est faite plus complète, on tend à attribuer les effets non désirés aux composants actifs de la Pénicilline.

Les indications concernant la fréquence de ces phénomènes et le moment de leur apparition diffèrent assez. Sur 124 malades traités à la Pénicilline, *Kolodny & Denhoff* ont trouvé des effets non-désirés chez 23 p. 100. En 16 p. 100, l'apparition en était immédiate, tandis que 7 p. 100 des malades ont accusé des symptômes tardifs, de 7 à 15 jours après l'administration du médicament. *Lyons* rapporte des cas d'urticaires chez 12 malades sur 209 soumis à un traitement pénicillinique, sans indication précise du moment de l'éruption. *Gordon* cite

¹ Conférence faite, avec quelques modifications, dans la Société d'Allergologie de Danemark.

3 cas sur 25 d'effets immédiats non désirés. Dans tous les cas de *Gordon*, le mode d'administration était par la bouche. *Mendell & Prose* notent des incidents, apparaissant de deux à neuf jours après la fin du traitement, en $\frac{1}{2}$ p. 100 seulement. *Goldmann & Farrington* considèrent également l'hypersensibilité à la Pénicilline comme un phénomène assez exceptionnel.

En vue d'une série de conférences sur l'hypersensibilité à la Pénicilline au dedans de diverses branches de la médecine, nous avons de notre côté fait le recensement de nos malades du service et de la polyclinique rapproché à des expériences faites d'autres parts.

Le caractère que revêtent les effets nuisibles est conditionné, dans une certaine mesure, par la voie d'administration de la Pénicilline. Par cette raison, nous avons jugé utile de faire la distinction entre le traitement par injection et le traitement local comprenant administration par pulvérisateur, en pastilles ou en forme de poudre.

En ce qui concerne le traitement par injection, nous n'avons eu qu'un seul cas indubitable :

Garde-malade, âgée de 28 ans, avec un ostéome dans le sinus frontal gauche. Elle n'avait pas été traitée par la Pénicilline auparavant; de même que rien dans ses antécédents n'indiquait des prédispositions allergiques. Lors de l'opération pour le dit ostéome, il se produisit quelques petites écorchures dans la dure-mère, à cause desquelles on donna 200.000 unités Pénicilline (Leo) par voie I. M. deux fois par jour. A part d'une légère élévation de température les premiers jours suivant l'opération, il n'y avait pas de gênes postopératoires. La Pénicilline fut arrêtée 7 jours après l'intervention, la malade ayant reçu 2.800.000 U. au total.

Une semaine après la dernière injection apparut un exanthème en forme de grain de millet, confluent, prurigineux, localisé aux coudes et aux fesses, de caractère urticarien et accompagné d'une faible montée de température. L'exanthème s'étendit au visage, où il y avait oedème autour des yeux et de grandes papules pâles, en partie confluentes. Une semaine

après l'éruption de l'exanthème, celui-ci commença à disparaître spontanément, Ephédrine, Antistine et injection intra veineuse de gluconate calcique à 10. p. 100 s'étant montré sans effet sur l'exanthème très pénible.

Ce cas personnel ressemble étroitement à d'autres observations de hypersensibilité après injection Pénicilline faite pour des affections otologiques :

Auteurs	Diagnostic	Dose	Apparition des effets seconds
Rajskjær & Huseby	Phlegmon parapharyngien	1.180.000	Tardive
	Otite moyenne supp. aiguë	400.000	Tardive
	Laryngite phlegmoneuse	980.000	Tardive
Roesgaard	Otite moyenne supp. aiguë	1.200.000	Tardive
	Abcès péri-amygdalien	100.000	Immédiate
Meulengracht	Pansinusite aiguë	1.800.000	Tardive

A cause des avantages bien évidents que présente l'administration orale de la Pénicilline, *Gordon* l'a essayée en 25 cas de différentes maladies oto-rhinolaryngologiques. Il donnait des comprimés de Pénicilline de calcium à raison de 25.000 U. en association avec des agents qui devaient neutraliser l'acidité de l'estomac. L'efficacité de la Pénicilline introduite par cette voie n'était pas démonstrative, et la médication donnait lieu dans les 12 à 48 heures au développement d'un exanthème prurigineux chez trois des malades (12 p. 100).

L'éruption urticarienne disparaissait comme dans les cas ci-dessus rapportés pour la plupart spontanément.

Après la Pénicillinothérapie par pulvérisateur, on a noté des effets non désirés chez les malades suivant :

Malade, 35 ans, atteint de pharyngite aiguë. On donna de la Pénicilline par spray (1000 U./ millilitre) toutes les deux heures. Après cinq jours, le malade se plaignit d'avoir la langue sèche, et la coloration de celle-ci devint chocolat. Après cessation du traitement pénicilliné, la langue redevint normale au bout de 10 jours.

Homme de 23 ans avec amygdalite aiguë et rhinopharyngite. Le traitement consistait en administration de pénicilline par pulvérisateur (5000 U./millilitre) toutes les deux heures. Après cinq jours, mélanoglossite et diarrhée. La diarrhée a cessé peu de temps après l'arrêt de la médication. La langue devint normale après quelques semaines.

Signalons enfin deux malades traités avec de la Pénicilline par spray pour une bronchite. Tous les deux ont développé une stomatite avec hyperhémie de la muqueuse accompagnée de douleurs cuisantes. Les symptômes disparurent après la suspension du traitement.

Les faits sus-mentionnés s'accordent parfaitement avec les expériences de *Goldmann & Farrington*, *Liebmann*, *Scheinberg* et *Schwartz*. Sur 17 malades traités par pulvérisateur, *Schwartz* a trouvé 1 cas de mélanoglossite et stomatite et 1 qui avait développé des urticaires. *Liebmann* met au point les observations de *K. A. Jensen* qui prétend avoir trouvé des cas de stomatite après administration de Pénicilline par voie buccale pendant 4 à 5 jours. Sur 41 malades, *Liebmann* avait 9 cas de stomatite, dont les 8 étaient apparus après un traitement de plus de 10 jours.

En parlant de ce mode d'administration, il est bon de noter qu'il peut également causer une hypersensibilité chez le médecin traitant. L'un des médecins attachés au service était incommodé, à des intervalles réguliers, d'une obstruction nasale. Petit à petit, il se rendit compte de ce que les symptômes nasaux apparaissaient chaque fois qu'il avait traité un malade avec le pulvérisateur de Pénicilline. Les vapeurs de Pénicilline suffisaient à opérer la sensibilisation. Ce phénomène est souligné par *Mac Innis*, qui constata obstruction nasale chez deux infirmières, dont l'une s'occupait à la préparation des solutions pénicillinées, tandis que l'autre se trouvait seulement dans la même pièce.

Incidents de la Pénicillinothérapie appliquée en forme de pastilles :

Femme de 75 ans atteinte d'une stomatite ulcéreuse. La

malade fut traitée avec des pastilles à la Pénicilline à raison de 1000 U. Au bout de deux jours, apparut une glossite, et la langue prit un aspect ressemblant à la peau des framboises (muqueuse linguale à papilles rouge-foncé et gonflées) accompagné d'une sensation de cuisson. Les symptômes disparurent au bout de deux semaines après arrêt de la médication.

Femme, âgée de 66 ans, avec stomatite ulcéreuse. Le traitement était identique à celui appliqué dans le cas précédent. Après deux jours, elle présenta exactement les mêmes symptômes qui disparurent au bout de deux semaines, après qu'on eût cessé la Pénicilline.

Otologiste, 35 ans, avec amygdalite aiguë. Il prenait environ 13 pastilles à la Pénicilline durant la journée. Au bout de deux jours, il ressentit une sensation très pénible de cuisson et de brûlure dans la bouche, particulièrement accentuée aux repas. Après cessation des pastilles, les troubles disparurent au bout d'une semaine.

La littérature parle peu de ce phénomène, nous n'avons trouvé que quelques rares cas, e.a. par *Goldmann & Farrington* qui décrivaient l'occurrence rare d'une hypersensibilité à la Pénicilline en forme de rougeur et d'enflure de la muqueuse buccale après l'emploi de pastilles à la Pénicilline.

Nos recherches bibliographiques ne nous ont pas permis de trouver des cas d'effets seconds après saupoudrage de cavités opératoires avec de la Pénicilline. Voici l'histoire clinique de notre cas personnel :

Le malade, garçon carpentier, âgé de 24 ans, fut hospitalisé pour une otite chronique suppurée, avec cholestéatome. Il n'avait pas été traité à la Pénicilline auparavant.

A l'entrée du malade, il y avait sécrétion fétide dans le conduit droit, une défectuosité située en arrière sur le bord du tympan avec du tissu granulé et cholestéatome et signes cliniques d'une fistule labyrinthique.

Lors de l'opération radicale de l'oreille moyenne, on enleva du tissu cholestéatomateux et un polype de granulation dans l'antre mastoïdien. Il existait une ostéite ayant produit une

fistule longue de 3 mm sur la capsule du canal demi-circulaire horizontal. Après plastique du conduit auditif, on poudra la cavité opératoire avec de la Pénicilline. Tamponnement.

A cause de la fistule labyrinthique, on donna 200.000 U. de Pénicilline deux fois par jour par voie intramusculaire. On cessa la Pénicilline au bout de 7 jours, après avoir donné au total 2.800.000 U. par voie I. M.

Les soins postopératoires étaient ceux d'usage. Après le premier pansement, ablation de la mèche, irrigation au sérum physiologique, essuyage précautionneux et insufflation de poudre pénicillinée. Cependant, au bout de quelques jours, on remarqua de la rougeur et des signes d'irritation de la peau du conduit, sur l'oreille externe et autour de celle-ci. Comme on avait déjà constaté des modifications indentiques chez d'autres malades soumis au même traitement, on cessa le saupoudrage, après quoi la cavité opératoire prit un aspect plus net, tandis que le peau de l'oreille et celle du conduit devinrent parfaitement normales.

Lors d'un pansement une semaine plus tard, on a de nouveau par erreur insufflé de la poudre pénicillinée dans la cavité opératoire. Aussitôt après, le malade accusa des démangeaisons dans le conduit, et le même soir apparurent sur la peau du figure, sur le tronc et les extrémités des tâches éparses, de la taille d'une paume d'enfant à peine, à papilles folliculaires, concurremment avec des tâches diffuses, d'aspect urticarien, rosées et prurigineuses. Le lendemain, la cavité opératoire était très rétrécie par suite d'enflure tissulaire et d'hyperhémie. Le service dermatologique ne pouvait décider, d'après le seul aspect de l'éruption, s'il s'agissait d'un exanthème pénicillinique. La cutiréaction était négative. L'exanthème disparut d'ailleurs au bout de quelques jours sans traitement spécial.

Dans l'observation ci-dessus rapportée, il pourrait s'agir — comme on a d'abord présumé — d'une réaction au traitement local de Pénicilline dans un organisme préalablement sensibilisé par des injections, mais, il pourrait aussi être question d'une réaction tardive aux injections. Or, le fait que

ce malade avait déjà souffert d'exanthème et qu'un nouveau saupoudrage fut suivi de près de démangeaisons dans le conduit et d'urticaires universelles, nous incline à regarder le cas comme l'expression d'une réaction au traitement local.

On n'a pratiqué des tests cutanés que sur quelques malades. La réaction était négative pour tous. Dans des cas d'incidents survenus après un traitement par l'Erosol, *Schwartz* a trouvé la réaction intraderme négative chez l'un des malades, tandis qu'elle était positive dans les deux observations sus-citées de *Goldmann & Farrington*. Le test cutané fait par *Roesgaard* était négative chez tous les malades « essayés » après traitement par injections à la suite desquelles étaient survenus des effets non désirés. Après test intraderme, le premier malade présentait une réaction positive, tandis que chez les deux autres elle était négative. *Røjskjær & Huseby* indiquent d'avoir trouvé une réaction négative chez leurs trois malades après des tests intradermes à la Pénicilline.

On peut diviser les effets seconds en deux groupes nettement différents suivant que la pénicillino-thérapie a été localisée à la cavité buccale (spray et pastilles) ou qu'elle a été universelle (injections et administration par voie orale). Dans le premier cas, les effets non désirés consistent en glossite et en stomatite, affections provoquées, selon *K. A. Jensen* et *Scherwin*, par une infection due au colibacille appartenant à une classe résistante à la Pénicilline et qui pourrait par conséquent prendre le dessus et acquérir une action pathogène. *Scherwin* a régulièrement trouvé une croissance abondante de colibacilles dans les glossites pénicilliniques.

Après l'administration par injection, les manifestations prennent généralement la forme d'œdèmes et d'exanthèmes de nature urticarienne. On tend à expliquer comme allergiques ces phénomènes, bien que les tests cutanés soient négatifs dans la plupart des cas.

Le caractère des urticaires et l'apparition ordinairement tardive de celles-ci sont autant de faits nous portant également à croire qu'il s'agirait de phénomènes allergiques. La con-

statation d'une récidence d'épidermophytic après un traitement pénicilliné témoigne dans le même sens. Dans ce dernier cas, l'organisme a été sensibilisé au Pénicillium.

Les divers incidents de la Pénicillino-thérapie n'ont guère beaucoup d'importance, comme l'a signalé *Roesgaard*, et ne doivent pas, le cas échéant, faire hésiter à la continuer dans des cas d'indication formelle.

Le traitement le plus simple de ces réactions non désirées est l'arrêt de la médication. Étant donné cependant, que les exanthèmes urticariens sont le plus souvent accompagnés de prurit insupportable, on a essayé différentes thérapeutiques plus actives : 1) Injections de calcium, 2) préparations d'Ephédrine et d'adrénaline, 3) antihistamines (Amidryle, Bénadryle et pyribenzamine) et 4) Procaïne. De toutes ces différentes préparations, Amidryle a donné les meilleurs résultats.

EN RÉSUMÉ

L'auteur cite un nombre d'observations dans lesquelles sont apparus des effets non désirés après l'emploi de Pénicilline en oto-rhino-laryngologie. Il précise le fait que le caractère des incidents est conditionné à la voie d'introduction de la Pénicilline, celle-ci pouvant être administrée en forme d'injection, comme pastilles, par spray ou pulvérisée en poudre. Les résultats des tests cutanés et enfin la symptomatologie et la thérapeutique sont mentionnés.

SUMMARY

By-effects of administration of penicillin in otorhinolaryngology.

The present investigation within the field of otorhinolaryngology is one of a series to determine the hypersensitiveness to penicillin in the cases of various specialists.

It appears that the nature of the by-effects are dependent on the mode of administration of penicillin; distinction is

made between treatment by injections and local treatment, the latter comprising spray treatment, lozenges, and powdering.

Treatment by injections mainly causes most irritating, universal, papuliferous exanthems with late appearance.

Spray treatment results in glossophytia, accompanied by dryness, whereas the lozenges cause glossitis ("raspberry tongue"), accompanied by strong smarting pains, especially intense during mastication.

Finally, mention is made of a patient who, on penicillin powdering of his radically operated middle ear, immediately presented distinct signs of penicillin sensitization.

Cutaneous tests yielded negative results.

Treatment took the form of cessation of penicillin administration.

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CONTROL EXAMINATION OF THE SPECIFICITY OF SPECIFIC DESENSITIZATION IN ASTHMA

By

EGON BRUUN

In the course of time asthma has been subjected to an almost interminable number of therapeutical methods, and even if we confine ourselves to considering only the forms of treatment employed for the time being, we will soon find that they are by no means few. Mention may be made at random of climatic treatment, shock treatment, vaccine therapy and pyretotherapy, remedial exercise, tuberculin and sulphur treatment, antiallergic therapy, antihistamine substances, and hypnosis, to take only the most common. It holds good of all these methods of treatment that, so far, none of them has with absolute certainty become generally accepted as the best form of therapy; but it may undoubtedly be said that the view that asthma is a disorder of primarily allergic determination is gradually becoming more widely accepted and that, consequently, we must await with increasing interest the results of the anti-allergic treatment, the most rational exponent of which is the specific desensitization.

After the specific treatment of hay fever had been introduced by Noon and Freeman in 1910-11 with so excellent a result, the idea almost suggested itself of attempting specific desensitization of *asthma* as well, in cases where a specific allergen could be demonstrated as the causative agent (Cooke, 1918); and in 1921 Caulfield was able to communicate the first results of specific desensitization of asthma-

tics, and the results were definitely promising. Later, this form of treatment met with difficulties and has hardly yet been placed where it belongs, but the last decades have seen this therapy become of increasingly greater interest. The results that can be achieved by specific desensitization of asthma are stated somewhat differently, but on examination of the results attained in Scandinavia (Salén, Stockholm; Flensburg and Bruun, Copenhagen) the figures relating to the patients who have distinctly improved in the course of a period of observation of about one year will be seen to be fairly identical, about 75 to 85 per cent. With regard to the effect on the *long-view* (3 years), E. Henriksen found a permanent improvement in 59 per cent. but considers that this figure will have to be somewhat reduced, because factors other than the specific desensitization may be active.

In spite of the fact that there are numerous publications on specific desensitization of asthmatics, the literature contains few, if any, unquestionable control examinations. It is known that 20-40 per cent. of all asthmatic children recover before puberty (1,5), a fact to which we should pay the greatest attention when judging the results of the various methods of treating infantile asthma. In a paper which has not yet been published, I believe to be able to demonstrate that the prognosis in *adult* asthmatics, with a seven years' period of observation, is by no means so favourable in the case of a spontaneous course—less than 10 per cent. will recover "spontaneously". Apart from this information, we lack reliable control examinations.

At the Medical Out-Patients' Department of the University Hospital of Copenhagen, where, since 1941, the specific desensitization of asthma has been systematically employed whenever possible, a thorough control examination of the specificity of the specific desensitization was, therefore, considered necessary. We all agree that asthma is to a certain extent a disease of psychic determination—or may at any

rate be so—, and that treatment at a special clinic for asthmatics may act as a sort of psychotherapy. Consequently, we considered that we had to undertake these control examinations ourselves, and they have been guarded with the closest secrecy—not even the nursing staff and the subordinate members of the medical staff knowing anything about the experiment.

In the course of a definite period—from the middle of 1945 to the beginning of 1947—we treated every other patient who suffered from house-dust allergy with the specific extract, and the remaining patients with suspension liquid containing no allergen, but bottled and labelled exactly like the specific extract, apart from the fact that it was provided with a minute descriptive mark which only two of the physicians knew of. Patients with odd case record numbers were treated with the specific extract, and patients with even case record numbers were treated with the suspension liquid. The practical procedure was as follows: Two extracts which looked quite alike, the specific and the suspension liquid, were made for each patient; after the diagnosis had been established by means of the specific extract, I replaced the latter with the suspension liquid in the case of patients with even case record numbers. These patients were then treated with the suspension liquid, which is just a slightly alkaline aqueous liquid, for just the same period, in exactly the same manner, and by the same physicians as the other patients. After the treatment had been concluded, a statement of the results was prepared, and after a certain period of observation—from 3 to 12 months—the patients were asked to appear for after-examination. The patients were all adults who had been suffering from asthma for a long time.

The results will appear from Table I.

The first group—patients under specific treatment—comprises 100 patients, as compared to 89 in the group of controls. This is due to the fact that, in order to exclude the effect on asthma of seasonal change, the two series of experiments were undertaken simultaneously during exactly the same

TABLE I

Results 3 to 12 Months after End of Treatment.

	Symptom-free	Improved	Unchanged	Worse	Treatment interrupted	Total no. of patients
Specific desensitization ...	13=13.6 %	61=64.2 %	18=18.9 %	3= 3.2 %	5	100
	$78 \pm 4.3 \%$		$22 \pm 4.3 \%$			
Controls ...	3= 3.7 %	25=30.5 %	45=54.9 %	9=11.0 %	7	89
	$34 \pm 5.3 \%$		$66 \pm 5.3 \%$			

period, and when one group—which thus became that submitted to specific desensitization—reached the number of 100 patients, the examination was concluded.

It will appear from Table I that specific desensitization produced a distinct improvement in 78 per cent., whilst 22 per cent. did not improve. The probable mean error of the mean figure of these two values is ± 4.3 per cent. In the group of controls, improvement took place in 34 per cent., and no effect was produced in 66 per cent., the mean error of the mean figure being ± 5.3 per cent. There is thus a great difference between the results obtained in the two groups, but at the same time it is of great interest to observe that one-third of the control patients improved—even with so long a period of observation as one year—solely by means of injections of a slightly alkaline liquid. This means that we must reckon with the fact that—if carried out with the complete apparatus employed at an asthma consultation—*any new method of treatment of asthma will be followed by improvement in about one-third of the patients irrespective of the somatic effect of this treatment.* But it does *not* mean that one-third will get rid of the disease; for the proportion freed of symptoms is extremely small, only about 3.7 per cent., a figure that is well in keeping with the pessimistic view of the prognosis for the spontaneous course in adult asthmatics

that has already been mentioned. According to our present knowledge, spontaneous recovery can doubtless be ignored as an essential factor in the case of adults only, but there is probably a certain tendency towards "spontaneous" variation also a positive direction, corresponding perhaps, in magnitude to the 11 per cent. who get worse. It can therefore hardly be said that the psychological factor of the treatment in question alone produces an improvement in 34 per cent., but the 34 per cent. must be considered a maximum figure. Nor can it be said that the specific desensitization produces improvement in only $87-34 = 44$ per cent., for (1) the 34 per cent. is a maximum figure, and (2) the improvement in some of the 78 per cent. is undoubtedly due *both* to psychological and humoral factors.

It will moreover appear from Table I that 22 per cent. did not improve by means of specific desensitization, whilst the corresponding figure in the group of controls was 66 per cent. There is thus every reason to continue and intensify the specific anti-allergic treatment.

In order to ascertain that no special factors, in particularly the common infectious complications in asthma, might have given an unequal distribution of patients in the two groups of the material, it was examined whether the two groups were comparable in that respect.

It proved that of 95 specifically treated patients 47 were suffering from chronic infections of the respiratory tract (including the sinuses), while in 48 patients no such complications could be demonstrated. In the control-material consisting of 82 patients, infections caused complications in 40 cases, while the other 42 were free of complications. Thus there seems to be a fairly equal distribution of infectious complications within the two groups of patients.

In studying the result of the treatment in the groups of complicated and non-complicated asthma, it will be seen from Table II that there is no definite difference. In the specifically treated group, 33 complicated and 28 non-complicated cases showed improvement, i.e. almost the same result in complica-

TABLE II
Distribution of the Infectious Complications within the two Groups.

Specific Desensitization.

	No. of patients	symptom-free	improvement	Unchanged	Worse
+ complications	47	1	33	11	2
— complications	48	12	28	7	1
Total	95	13	61	18	3

Controls.					
+ complications	40	0	9	25	6
— complications	42	3	16	20	3
Total	82	3	25	45	9

ted as in non-complicated cases, and this holds for almost all the figures. This means that the effect of the specific desensitization in cases of true allergic asthma must generally be considered independent of the complicating infections (in this connection it must be pointed out that there were no cases of bronchiectases in the material). However, in one direction there seems to be a difference: Among the infectiously complicated cases only one patient was freed of symptoms, but among those free of complications this result was achieved in 12 cases. This may suggest that a really fine result in the majority of cases is obtainable only with patients who do not suffer from complicating infections.

In 28 patients we were able to carry through a kind of double control, as these 28 were first treated with the suspension liquid and then—after a suitable period of observation—with the specific allergen. The results will appear from Table III which shows that 22 out of 28 patients remained uninfluenced by treatment with suspension liquid, whereas in the *same group of patients* only 7 out of 28 did not improve after specific desensitization.

TABLE III

28 Patients first treated with Suspension Liquid ("Control") and then with Specific Desensitization.

	Control	Specific Desensitization
Symptomfree	0	2
Improved	6	19
Unchanged	19	5
Worse	3	2
Total of patients	28	28

Probable mean error on the mean figure $\pm 7.9\%$ and $\pm 8.3\%$.

CONCLUSION

The results of the above examination must be (1) that about one-third of all grown-up patients with long-standing asthma will improve for some time when they are no more than under the psychic impression that they are being given a rational asthma therapy, and (2) that the specific desensitization produces results far superior to those produced by this psychotherapy, as about 78 per cent. improve or are freed of symptoms by this treatment. These examinations have thus provided the basis of a quantitative estimate—with certain reservations—of the psychic factor in the treatment of asthma.

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SENSITIZATION TO PARA-AMINOSALICYLIC ACID

By
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Para-aminosalicylic acid (PAS), whose good therapeutic qualities in the treatment of tuberculosis have aroused a justified attention, is said to be remarkably free from injurious side-effects. *Vallentin* (1946), for instance, mentions the remedy as being quite harmless. Apart from gastrointestinal reactions only solitary cases of a slight irritation of the kidneys have been noticed. *Carstensen* (1948), also, had not observed any more remarkable side-effects. The usual dose has been 10-14 g daily, and the medicine has been given for periods of 3-4 weeks with an interval of one week between the periods. In an abstract in *Nordisk Medicin* in September of 1948, *Vallentin* says, that single cases of skin affections and agranulocytosis have also been observed. These complications, however, being very rare and in most cases of so mild a nature, they do not prevent the use of PAS in cases where it evidently is indicated.

In connection with PAS-treatment of Lupus erythematosus I observed a remarkable hypersensitivity to PAS in a female patient, born 1907.

DESCRIPTION OF THE CASE:

The patient has earlier been healthy, displaying no symptoms of allergy. In 1930, about 2 weeks after the birth of her first child, she developed lymphomatous swellings on the right side of the neck and in the axilla. They were

considered tuberculous, suppurated, were punctured and treated with Roentgen rays. Simultaneously with this, or maybe a little earlier even, she developed Lupus erythematosus on the face. (She had some years before exposed herself to intense sunbaths.) The rash disappeared with Bi-injections. In the late Winter of 1941 the rash reappeared after a trip to the mountains (sun and wind) and has since then not responded to repeated attempts with Bi, Nicotilamide, gold, Neo-Halarsine and carbon dioxide. Thus the patient still has numerous reddish plaques on her nose, cheeks and forehead.

On April 29, 1949, a treatment with PAS (Parasal tablets) was begun, first with 6 g daily, after May 2, 1949, with 8 g daily. At the beginning she tolerated the remedy without side-effects. After 6-7 days' treatment the effect was very promising, surpassing by far all previous methods of treatment. The plaques had grown pale and, as it were, been turned into a lifeless layer of scales, peeling easily, revealing a smooth, pink, somewhat brownish skin on a level with the rest of the skin. All unevenness had disappeared. Cosmetically disturbing now, in the head, were a couple of scars only, caused by an earlier treatment with carbon dioxide.

On May 8, 1949, the patient rode in an open car in a "damned cold wind" and contracted a rather typical cervical and lumbal myalgia with headache and stiffness in the muscles of neck and back.

As the headache did not disappear she took, on May 17 and 18, 6 tablets of Sodium salicylate daily, simultaneously with the PAS-medication (the dosage of which had continued uninterruptedly since April 29, that is for 19 days).

On May 18 she suddenly felt pricking and numbness on the inner side of the thighs and the upper arms, and in the lips. Shortly after that she had violent chills (temperature over 39° C), her teeth chattering so that she could hardly speak. At the same time she experienced nausea and a most violent pain in her back, especially in the sacro-lumbal region, radiating down along the buttocks and the back side of the legs. Within half an hour her eyeballs became quite bloodshot, she had some difficulty in breathing, and developed an asthmatic cough with somewhat foamy sputum. About two hours later she had an almost general erythrodermia on large parts of her body. The PAS-treatment had to be interrupted.

During the attack tenderness was noted on palpation of the liver and the right kidney. The patient had vesical tenesms. The urine, however, was clear, sour, alb. —, Nylander —, Ehrlich —, Schlesinger —, iodine test —. In the sediment solitary erythrocytes (0-2 in the range of sight), leucocytes (0-2) and epithelial cells. No bacteria.

Afterwards some itching in the back, in fingers and feet. Patellar reflexes normal, sedimentation rate 11 mm. A doctor she consulted gave her an injection of morphine-scopolamine and ephedrine perorally. The eruption disappeared within a few days.

As the patient had earlier tolerated aspirin well, it seemed most probable that the angioneurotic attack was a manifestation of a sensitization to PAS.

When the patient had been free from symptoms for about 12 days, I gave her half a tablet (0.5 g) of Parasal to swallow on June 1, 1949. The result was soon apparent. After 10 minutes she felt prickings on the inner side of the thighs, on the back of her hands and in the throat. At first she was quite pale. Some minutes later her eyes became bloodshot, she developed an asthmatic cough and her voice got quite hoarse. Fortunately the cough and hoarseness soon became better (she was given 2 tablets of Pyribenzamine). But the patient also had chills, sensation of heat in the face, nausea, sweating on the forehead, headache and the same pain in the back and the extremities, although this time less intense than on the first attack. Her face even now showed redness with slight oedema of the eyelids, and an erythematous, or partly morbilliform rash was visible on the extremities, most pronounced on the inner side of the thighs. She was given an injection of adrenaline, and for the pain I was compelled to give her an opiate, too.

DISCUSSION

In this case PAS seemed to be of great value in the treatment of Lupus erythematosus. After 19 days, however, the patient had become hypersensitive to PAS, and reacted subsequently even to a small dose (0.5 g) of the medicine with angioneurotic symptoms: chills, fever, nausea, hoarseness, asthmatic cough, conjunctivitis, erythematous eruption, headache and intense pain in back and legs.

The symptoms of intolerance were threatening enough to leave out every thought of continued treatment.

Continued observations are necessary before judging whether such a sensitization to PAS is more common among patients suffering from Lupus erythematosus, or whether my case was a mere exception. No patch tests were carried out, nor Mester's test either. (According to Bosco and Cecere this intradermic test with salicylic acid is said to be positive in Lupus erythematosus in 68.7 per cent cases.)

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STUDIES ON THE EFFECT OF ANTISTINA, AMIDRYL AND PYRIBENZAMINE ON THE PRAUSNITZ-KÜSTNER REACTION¹

By

THORKILD FRIIS

The effect of various antihistamines on urticaria has been described in numerous reports, according to which it may be possible to obtain improvement of the affection in about 50-70 % of the chronic cases and about 80-90 % of the acute cases, the favorable effect applying both to the itch and to the urticarial reaction (1, 3, 7, and 11).

In this connection it will be of interest to elucidate how various antihistamines act upon experimentally produced urticarial hypersensitiveness. This condition was produced by employment of the Prausnitz-Küstner experiment first described in detail by Prausnitz & Küstner (8) in 1921. The technique of this experiment was as follows: A small amount of serum derived from a strongly hypersensitive allergic is injected intracutaneously on a normal person, sensitizing the surrounding skin area. 24 hours later the allergen is injected

¹ The studies here reported were carried out with a view to a prize problem of 1948 at the University of Copenhagen: "Investigation is wanted into the effect of substances presumably antagonistic to histamine on experimentally produced allergic hypersensitiveness of eczematous and urticarial nature."

Antistina (Ciba, Switzerland) = N-benzyl-N-phenyl-aminomethylimidazolin.
Amidryl (Medicinalco, Denmark) = Benadryl (Parke, Davis and Co., U.S.A.)

= β -dimethyl-aminoethylbenzhydrylether-hydrochloride.

Pyribenzamine (Ciba, U.S.A.) = N-benzyl-N- α -pyridinaminoethyl-dimethylamine.

into the sensitized skin area. After this, if the test turns out positive, a typical urticarial papule appears at the site of the injection. Thus, the reaction is a local reproduction of the allergic mechanism under experimental conditions as pure as possible.

The literature on the effect of various antihistamines on the Prausnitz-Küstner reaction is only scanty, and the results are divergent. Jadassohn & Diedey (4) have looked into the effect of antistina, antergan and neoantergan upon the reaction when this is produced after ingestion of large therapeutic doses. It proved possible always to obtain a positive reaction, and the authors think that there is no demonstrable inhibition.

Vallery-Radot, Maurice and Halpern (13) gave large doses of antergan and neoantergan prior to the tests in six cases. In 5 of them the reaction turned out absolutely negative, and in one case it was moderately inhibited.

Nexmand & Sylvest (6) gave 0.15 g. amidryl per os, and the test was performed before the ingestion of this substance and then every 15 minutes in the following two hours. The authors were unable to demonstrate any inhibition of the reaction whatever. Arbesman *et al.* (2) examined the effect of pyribenzamine on the Prausnitz-Küstner test, and they found the reaction to decrease when the patients had taken 100 mg. of the remedy by mouth one hour before the test.

EXPERIMENTAL TECHNIQUE

The experiments were carried out in part with serum from a patient suffering from bronchial asthma produced by soy bean meal, and in whom the skin tests with soy meal extract were strongly positive, partly with employment of serum from hay fever patients. Venesection was performed on the soy meal allergic, and 500 cc. blood was evacuated. The serum from this blood was filtered through a bacterium-proof filter. The serum was then transferred to ampules and was now ready for use.

The serum from hay fever patients was employed in the form of dry serum¹. This dry serum had been prepared from 7000 cc. blood from altogether

¹ This dry serum was obligingly placed at my disposal by Dr. Michael Schwartz.

505

1

1

7

TABLE 1
Size of papules before and after intake of antistina.

Exp. No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of antistina	Size of papules after intake of antistina
<i>Soy bean meal.</i>					
1	0.2 g.	1 hour	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	9 \times 11 mm. 8 \times 10 mm. 0	12 \times 12 mm. 10 \times 7 mm. 0
2	0.2 g.	1 "	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	17 \times 13 mm. 9 \times 10 mm. 0	19 \times 13 mm. 13 \times 10 mm. 0
3	0.2 g.	2 hours	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	12 \times 13 mm. 13 \times 11 mm. 0	18 \times 11 mm. 13 \times 8 mm. 0
4	0.2 g.	2 "	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	14 \times 14 mm. 11 \times 7 mm. 0	12 \times 12 mm. 13 \times 13 mm. 0
<i>Pollen.</i>					
5	0.2 g.	3 "	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	13 \times 11 mm. 4 \times 9 mm. 0	8 \times 12 mm. 8 \times 5 mm. 0
6	0.2 + 0.2 g.	1 hour	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	17 \times 15 mm. 17 \times 14 mm. 0	13 \times 12 mm. 6 \times 8 mm. 0
7	0.2 + 0.2 g.	1 "	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	18 \times 12 mm. 12 \times 8 mm. 0	14 \times 12 mm. 13 \times 14 mm. 0
8	0.2 + 0.2 + 0.2 g.	1 "	1 $\frac{0}{\infty}$ 0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$	11 \times 12 mm. 15 \times 13 mm. 0	22 \times 13 mm. 13 \times 8 mm. 0
9	0.2 + 0.2 g.	2 hours	0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$ 0.001 $\frac{0}{\infty}$	14 \times 12 mm. 12 \times 11 mm. 0	13 \times 11 mm. 11 \times 9 mm. 0
10	0.2 + 0.2 + 0.2 g.	2 "	0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$ 0.001 $\frac{0}{\infty}$	12 \times 12 mm. 8 \times 8 mm. 0	9 \times 9 mm. 8 \times 7 mm. 0
11	0.2 + 0.2 g.	2 "	0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$ 0.001 $\frac{0}{\infty}$	9 \times 10 mm. 6 \times 9 mm. 0	9 \times 7 mm. 6 \times 6 mm. 0
12	0.2 + 0.2 g.	3 "	0.1 $\frac{0}{\infty}$ 0.01 $\frac{0}{\infty}$ 0.001 $\frac{0}{\infty}$	15 \times 10 mm. 8 \times 9 mm. 0	13 \times 14 mm. 13 \times 13 mm. 0

Amidryl Experiments.

The results are given in Table 2.

In the first four experiments serum from the soy bean allergic was employed for the sensitization; in the remaining experiments, serum from the hay fever patients. These experiments proceeded exactly like the antistina experiments, only that in some cases 0.1 g. amidryl was given instead of 0.2 g. antistina.

TABLE 2
Size of papules before and after intake of amidrylin.

Exp.No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of amidrylin	Size of papules after intake of amidrylin
<i>Soy bean meal.</i>					
1	0.1 g.	1 hour	1 $\frac{0}{\infty}$	13×10 mm.	10×14 mm.
			0.1 $\frac{0}{\infty}$	9× 9 mm.	9×14 mm.
			0.01 $\frac{0}{\infty}$	0	0
2	0.1 g.	2 hours	0.1 $\frac{0}{\infty}$	12×12 mm.	13×13 mm.
			0.01 $\frac{0}{\infty}$	9×10 mm.	5× 8 mm.
			0.001 $\frac{0}{\infty}$	0	0
3	0.1 g.	2 "	0.1 $\frac{0}{\infty}$	10×15 mm.	4× 6 mm.
			0.01 $\frac{0}{\infty}$	8× 6 mm.	0
			0.001 $\frac{0}{\infty}$	0	0
4	0.1 g.	3 "	0.1 $\frac{0}{\infty}$	10× 9 mm.	14× 8 mm.
			0.01 $\frac{0}{\infty}$	6× 9 mm.	9× 5 mm.
			0.001 $\frac{0}{\infty}$	0	0
<i>Pollen.</i>					
5	0.1+0.1 g.	1 hour	1 $\frac{0}{\infty}$	13×16 mm.	12×14 mm.
			0.1 $\frac{0}{\infty}$	10× 9 mm.	12×14 mm.
			0.01 $\frac{0}{\infty}$	0	0
6	0.1+0.1 g.	2 hours	1 $\frac{0}{\infty}$	21×20 mm.	17×13 mm.
			0.1 $\frac{0}{\infty}$	8×13 mm.	13×11 mm.
			0.01 $\frac{0}{\infty}$	0	0
7	0.1+0.1 g.	2 hours	1 $\frac{0}{\infty}$	12×17 mm.	8×10 mm.
			0.1 $\frac{0}{\infty}$	12×14 mm.	6× 8 mm.
			0.01 $\frac{0}{\infty}$	0	0

TABLE 2 (cont.)

Exp.No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of amidrylin	Size of papules after intake of amidrylin
8	0.1+0.1 g.	2 "	1 ‰	17×16 mm.	19×10 mm.
			0.1 ‰	9× 9 mm.	8×10 mm.
			0.01 ‰	0	0
9	0.1+0.1 g.	2 "	1 ‰	19×14 mm.	7× 8 mm.
			0.1 ‰	8× 6 mm.	3× 6 mm.
			0.01 ‰	0	0
10	0.1+0.1 g.	3 "	1 ‰	12×10 mm.	12×10 mm.
			0.1 ‰	5× 6 mm.	9× 6 mm.
			0.01 ‰	0	0
11	0.2+0.2 g.	1 hour	0.1 ‰	11× 8 mm.	12×14 mm.
			0.01 ‰	6× 9 mm.	7×13 mm.
			0.001 ‰	0	0
12	0.2+0.2 g.	2 hours	1 ‰	17×17 mm.	13×13 mm.
			0.1 ‰	13×13 mm.	13×10 mm.
			0.01 ‰	8×13 mm.	8×14 mm.
			0.001 ‰	0	0
13	0.2+0.2+0.2 g.	1 hour	0.1 ‰	12×12 mm.	14×14 mm.
			0.01 ‰	11×11 mm.	8×12 mm.
			0.001 ‰	0	0
14	0.2+0.2+0.2 g.	2 hours	0.1 ‰	10×10 mm.	15×12 mm.
			0.01 ‰	7× 8 mm.	11×10 mm.
			0.001 ‰	0	0

From Table 2 it will be noticed that except in Exps. 3, 7 and 9 there was no definite diminution in the size of the papules after intake of amidryl. Further, the threshold was altered only in Exp. 3, in which it changed from 0.01 ‰ to 0.1 ‰. In no instance did the character of the papule undergo any change. Exp. 12 is reproduced in Fig. 2.

Pyribenzamine Experiments.

The results are recorded in Table 3.

Serum from the hay fever patient was used in all the experiments except Nos. 1, 4 and 5 in which the serum from the soy bean allergic was employed.

Pyribenzamine thus appears to have had the same effect in experiments 3, 6, 7, 11, 13, 14, 15 and 16.

It is to be mentioned at once that in no instance did the urticarial character of the papules undergo any decisive change. Here, too, the papules were plane, pale and irregular

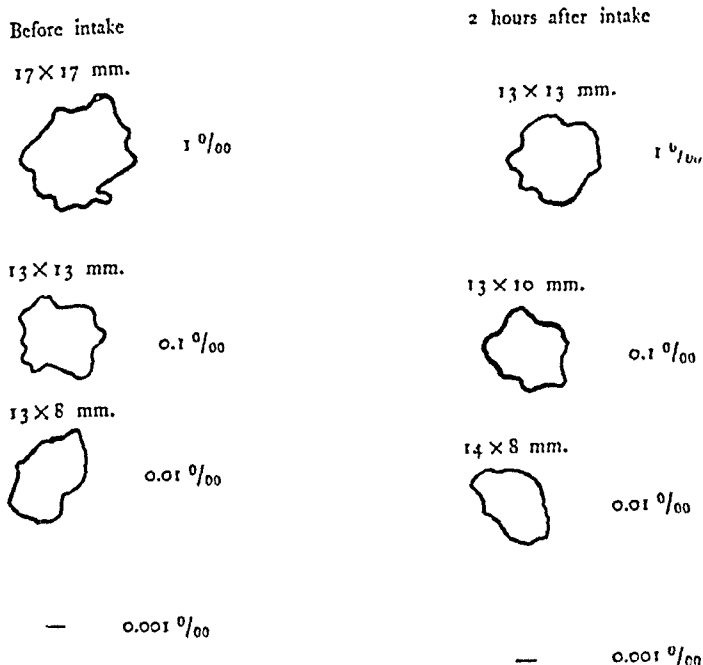


Fig. 2.

Prausnitz-Küstner reactions before and after intake of 0.2+0.2 g. amidryl by mouth.

in outline. In 8 of the 16 experiments the size of the papules diminished, and the reflex erythema was less pronounced. The threshold changed in 6 of the experiments. The reactions were depicted on transparent paper as usual, and Exp. 14 is reproduced in Fig. 3.

In no experiment was the antihistamine given parenterally.

In the literature the antihistamines are often stated to have a mitigating effect on the itch. In the present experiments, however, it is difficult to decide on this point, as the itch associated with the reaction here was only slight.

TABLE 3

Size of papules before and after intake of pyribenzamine.

Exp.No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of pyribenzamine	Size of papules after intake of pyribenzamine
<i>Soy bean meal.</i>					
1	0.1 g.	1 hour	0.1 ‰ 0.01 ‰ 0.001 ‰	16×7 mm. 8×5 mm. 0	15×11 mm. 13×10 mm. 0
<i>Pollen.</i>					
2	0.1 g.	2 hours	0.1 ‰ 0.01 ‰ 0.001 ‰	9×10 mm. 5×6 mm. 0	9×6 mm. 6×9 mm. 0
3	0.1 g.	3 "	0.1 ‰ 0.01 ‰ 0.001 ‰	9×13 mm. 6×10 mm. 0	8×5 mm. 0 0
<i>Soy bean meal.</i>					
4	0.2 g.	1 hour	0.1 ‰ 0.01 ‰ 0.001 ‰	12×10 mm. 6×10 mm. 0	11×11 mm. 12×10 mm. 0
5	0.2 g.	2 hours	0.1 ‰ 0.01 ‰ 0.001 ‰	12×10 mm. 6×8 mm. 0	9×6 mm. 8×9 mm. 0
<i>Pollen.</i>					
6	0.2 g.	3 "	0.1 ‰ 0.01 ‰ 0.001 ‰	8×14 mm. 7×10 mm. 0	6×8 mm. 0 0
7	0.05+0.05 g.	1 hour	0.1 ‰ 0.01 ‰ 0.001 ‰	14×14 mm. 10×12 mm. 0	8×10 mm. 8×10 mm. 0
8	0.05+0.05 g.	2 hours	0.1 ‰ 0.01 ‰ 0.001 ‰	10×15 mm. 7×8 mm. 0	16×11 mm. 6×7 mm. 0
9	0.1+0.1 g.	1 hour	1 ‰ 0.1 ‰ 0.01 ‰	11×14 mm. 7×12 mm. 0	11×16 mm. 7×8 mm. 0
10	0.2+0.2 g.	1 "	1 ‰ 0.1 ‰ 0.01 ‰	19×15 mm. 12×10 mm. 0	17×16 mm. 14×12 mm. 0

TABLE 3 (cont.)

Exp.No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of pyribenzamine	Size of papules after intake of pyribenzamine
11	0.2+0.2 g.	2 hours	0.1 ‰	12×15 mm.	5× 6 mm.
			0.01 ‰	11×10 mm.	0
			0.001 ‰	0	0
12	0.2+0.2 g.	2 "	0.1 ‰	17×13 mm.	14×14 mm.
			0.01 ‰	7×10 mm.	9×13 mm.
			0.001 ‰	0	0
13	0.2+0.2 g.	2 "	0.1 ‰	16×11 mm.	9× 5 mm.
			0.01 ‰	13×10 mm.	0
			0.001 ‰	0	0
14	0.2+0.2 g.	3 "	1 ‰	8×12 mm.	8× 4 mm.
			0.1 ‰	12×11 mm.	8× 5 mm.
			0.01 ‰	9×10 mm.	5× 6 mm.
			0.001 ‰	7× 8 mm.	0
			0.0001 ‰	0	0
15	0.2+0.2+0.2 g.	1 hour	1 ‰	24×16 mm.	13×11 mm.
			0.1 ‰	9× 9 mm.	5× 7 mm.
			0.01 ‰	0	0
16	0.2+0.2+0.2 g.	2 hours	0.1 ‰	9×14 mm.	8× 8 mm.
			0.01 ‰	6×10 mm.	0
			0.001 ‰	0	0

After this, some experiments were carried out to see how the Prausnitz-Küstner reaction might be influenced when the antihistamine was mixed with the allergen before its injection into the sensitized skin area. Jadassohn & Diedey (4) investigated how antistina, antergan and neoantergan influenced the reaction when one of these substances was mixed with the allergen before the injection. They found a pronounced inhibition in every instance.

The technique employed in my experiments was as follows:

On an experimental subject 6 skin areas—3 on the volar aspect of either forearm—were sensitized with dry serum from the hay fever patient. 24 hours later the reactions were induced by injection of 0.05 cc. of a mixture of equal parts of a 0.1 ‰ pollen solution and saline into the sensitized areas nearest

the wrist joints. Into the remaining 4 sensitized areas injections were given of 0.05 cc. of a mixture of equal parts of 0.1 ‰ pollen solution and 1 % solutions of antistina, amidryl, pyribenzamine and metadryl¹, respectively. The injections were given exactly in the same spot as the preceding sensitizing serum. For the sake of control, an injection of the allergen was also given outside the sensitized area. 15 min. later the resulting papules were depicted (Fig. 4). In those experiments where the mixture contained antihistamine, the papules

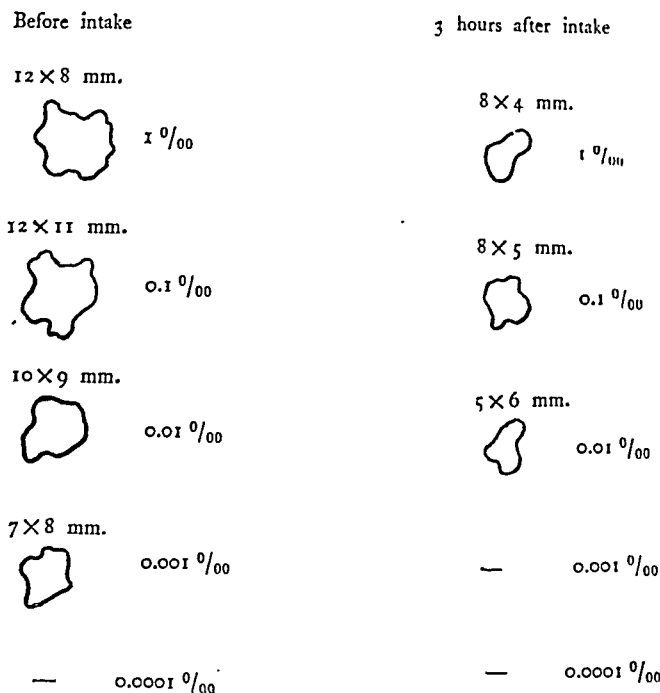


Fig. 3.

Prausnitz-Küstner reactions before and after intake of 0.2+0.2 g. pyribenzamine by mouth.

were greatly diminished and had changed in character. They were still plane, but more regular in outline; the color was reddish, and the surrounding redness was limited to an intensely red zone, 4-5 mm. wide, round the papules. There was no definite mutual difference between the antihistamine-treated papules.

The experiment was repeated—this time with employment of $\frac{1}{2}$ % solutions of antihistamines. Now 8 skin areas were

¹ Metadryl is an antihistamine produced by the Ferrosan medicinal factory, Copenhagen. It is near-related to benadryl, the only difference being that in the metadryl molecule one more methyl group is linked to the nitrogen atom.

sensitized instead of 6, 2 sensitized areas being injected with a mixture of 2 % procaine and 0.1 ‰ pollen solution, besides 2 % pantocaine and 0.1 ‰ pollen solution. The various antihistamines here employed have a rather pronounced local-anesthetic effect, which perhaps conceivably might have something to do with the inhibitory effect. Procaine and pantocaine, however, were not able to inhibit the size of the

17 × 11 mm.



0.1 ‰ pollen
+ 0.9 ‰ saline, equal parts

17 × 15 mm.



0.1 ‰ pollen
+ 0.9 ‰ saline, equal parts

5 × 6 mm.



0.1 ‰ pollen
+ 1 ‰ pyribenzamine, equal parts

5 × 6 mm.



0.1 ‰ pollen
+ 1 ‰ amidryl, equal parts

5 × 6 mm.



0.1 ‰ pollen
+ 1 ‰ metadryl, equal parts

5 × 6 mm.



0.1 ‰ pollen
+ 1 ‰ antistina, equal parts

Fig. 4.

Prausnitz-Küstner reactions produced with 0.1 ‰ pollen extract
+ antihistamines.

papules. The reactions were depicted as usual (Fig. 5). The antihistamine-treated papules were diminished this time, too, and also their character had changed in the same way as before. There was no definite mutual difference between the antihistamine-treated papules.

Now the question is what inferences may be drawn from these experiments in which antihistamine and allergen are mixed before the injection.

The inhibitory effect might simply be due to destruction or inactivation of the allergen by the antihistamine in the mixture, prior to the injection. Further, it is also conceivable that the inhibition may be due to entirely physical conditions. Intracutaneous injection of antihistamine gives rise to a papule

which does not increase in size, and which is surrounded by a zone of intense redness, presumably signifying a local irritation. The papule disappears rapidly, but the redness persists longer and is gradually replaced by brownish pigmentation, where the skin practically has lost its sensibility.

13 × 15 mm.



0.1 ‰ pollen
+ 0.9 ‰ saline, equal parts

17 × 15 mm.



0.1 ‰ pollen
+ 0.9 ‰ saline, equal parts

7 × 6 mm.



0.1 ‰ pollen
+ 1/2 ‰ pyribenzamine, equal parts

11 × 8 mm.



0.1 ‰ pollen
+ 1/2 ‰ amidryl, equal parts

7 × 7 mm.



0.1 ‰ pollen
+ 1/2 ‰ metadryl, equal parts

8 × 12 mm.



0.1 ‰ pollen
+ 1/2 ‰ antistina, equal parts

14 × 15 mm.



0.1 ‰ pollen
+ 2 ‰ procaine, equal parts

15 × 13 mm.



0.1 ‰ pollen
+ 2 ‰ pantocaine, equal parts

Fig. 5.

Prausnitz-Küstner reactions produced with 0.1 ‰ pollen extract
+ antihistamines.

The pigmentation and anesthesia may persist unchanged for several weeks. The hyperemic zone may possibly prevent the urticarial reaction from developing fully. Thus Török & Rajka (12) have reported that hyperemia—for instance, produced by heat applied to the skin—inhibits the development of histamine papules in the hyperemic area. In order to elucidate this question, the following iontophoretic experiments were carried out.

Iontophoretic Experiments.

These experiments were carried out with 5 % solutions of antistina, amidryl and pyribenzamine as hydrochloric salts. In these solutions the substances dissociate into antihistamine ions, with positive charge, and chloride ions, with negative charge. The electrode, consisting of a thin disc of lead, 2.5 cm. in diameter, was connected with the positive pole of the iontophoresis apparatus, and a circular piece of filter paper, moistened with the antihistamine solution, was placed on the electrode. Iontophoresis was carried on for 5 min. with a current of 2 milliamp. This gave rise to moderate redness and some miliary papules at the place of iontophoresis. Both the redness and the papules disappeared within 1-2 hours.

Altogether six experiments were carried out with the following technique.

In three places on the volar aspect of either forearm the skin was sensitized with dry serum from the hay fever patient as described before—at suitable intervals. 24 hours later the three antihistamines—pantocaïne, procaine, atropine sulphate—distilled water and tap water were introduced by iontophoresis, each to its sensitized skin area. Iontophoresis was carried out with all these substances in order to make sure that a possible antihistamine effect really would be due to antihistamine activity, not to the local-anesthetic effect of these substances or to atrophine effect (9), let alone the local irritation produced by the current. 1-2 hours later when the local effect of the current had subsided, the reactions were induced with the 0.1 % pollen extract solution, and the results were depicted 15 min. later. The experiments are recorded in Table 4.

In Exp. 1 iontophoresis was performed on the left arm with saline and a 2 % atropine solution. In both cases the positive electrode was employed so that sodium and atropine ions entered the tissue. Over the third sensitized area no iontophoresis was performed. On the right arm iontophoresis was performed with antistina, amidryl and pyribenzamine. The actual introduction of these three substances by iontophoresis was ensured by iontophoresis with histamine over a part of the area into which the antihistamine had been introduced. Corresponding to this area, some redness appeared, while corresponding to the rest of this area, over which histamine had been introduced by iontophoresis, vesiculation due to the histamine effect appeared about half a minute later. Then, one hour later, the allergen was injected into the six sensitized skin areas, and the reactions were depicted (Fig. 6).

From Fig. 6 it will be noticed that all the three antihistamine-treated

TABLE 4
Prasnitz-Küstner reactions in skin areas exposed to iontophoresis with antihistamines.

	Iontophoresis with	Size of reaction	Iontophoresis with	Size of reaction	Iontophoresis with	Size of reaction
Exp. 1	saline	14×12 mm.	—	16×15 mm.	2% atropine	12×12 mm.
	5% antistina	13×7 mm.	5% amidryl	16×8 mm.	5% pyribenz.	12×10 mm.
Exp. 2	2% pantocaine	10×12 mm.	—	10×12 mm.	saline	9×10 mm.
	5% pyribenz.	10×12 mm.	5% amidryl	10×12 mm.	5% antistina	10×16 mm.
Exp. 3	tap water	15×15 mm.	—	17×18 mm.	2% atropine	14×17 mm.
	5% pyribenz.	6×9 mm.	5% amidryl	10×12 mm.	5% antistina	12×14 mm.
Exp. 4	saline	15×19 mm.	tap water	12×16 mm.	—	16×12 mm.
	5% antistina	11×15 mm.	5% amidryl	12×12 mm.	5% pyribenz.	12×9 mm.
Exp. 5	tap water	19×19 mm.	2% procaine	13×13 mm.	—	15×17 mm.
	5% pyribenz.	11×7 mm.	5% amidryl	9×8 mm.	5% antistina	13×7 mm.
Exp. 6	saline	10×12 mm.	tap water	11×11 mm.	tap water	13×14 mm.
	5% pyribenz.	8×9 mm.	5% antistina	8×5 mm.	5% amidryl	8×13 mm.

papules were a little smaller than the other three reactions. The urticarial character of the papules and the time it took them to develop, however, were quite unchanged. The papules submitted to iontophoresis with atropine and with saline were not smaller than the papule which had not been exposed to iontophoresis.

In Exp. 2 iontophoresis was carried out with saline and a 2 % pantocaine solution, besides the three antihistamines. Here, too, the electrode was made

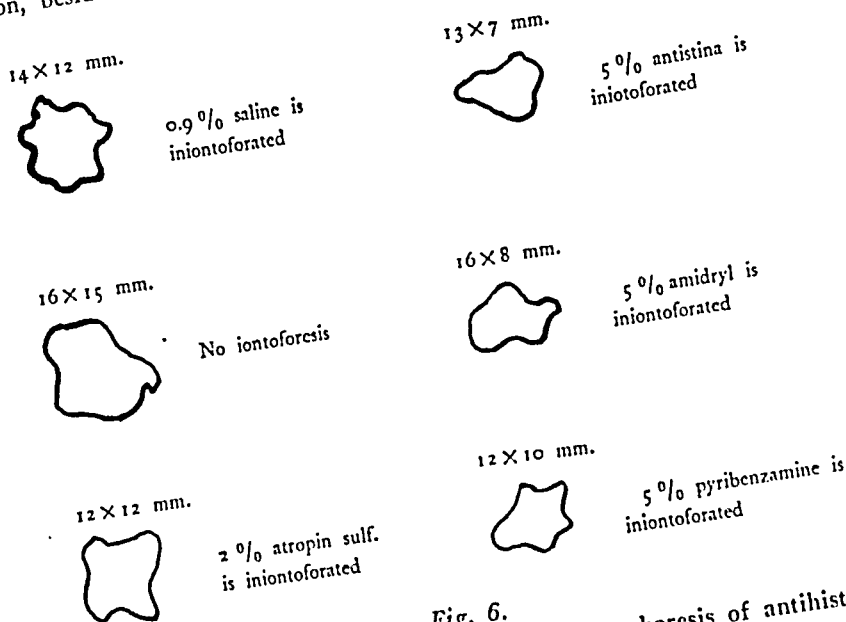


Fig. 6.
Praisnitz-Küstner reactions in skin areas with iontophoresis of antihistamines.

positive, so that the pantocaine ions might enter the tissue. There was no guaranty, however, that this actually did take place. Thus, no local anesthesia appeared, corresponding to the antihistamine areas. There is no reason to think, however, that some pantocaine ions would enter into the tissue. The reactions were induced as usual, but in this experiment there seemed not to be any definite difference in the size of the papules. Possibly this may be due to the circumstance that here the allergen was injected as early as 20 min. after the iontophoresis, i.e., before the local irritation had subsided completely. Thus the remaining hyperemia corresponding to the sites of iontophoresis may have had a disturbing effect.

Table 4 gives also the results of Exps. 3, 4, 5, and 6. The antihistamine-treated papules, on the whole, were smaller than the papules which had not been exposed to iontophoresis or had been submitted to the influence of tap water, saline, atrophine sulphate, procaine or pantocaine.

The results obtained in Exp. 3 are reproduced in Fig. 7. In this experiment pyribenzamine appears to have been superior to amidryl and antistina in this respect. In the remaining 5 experiments there appears to have been no definite mutual difference between the three antihistamines.

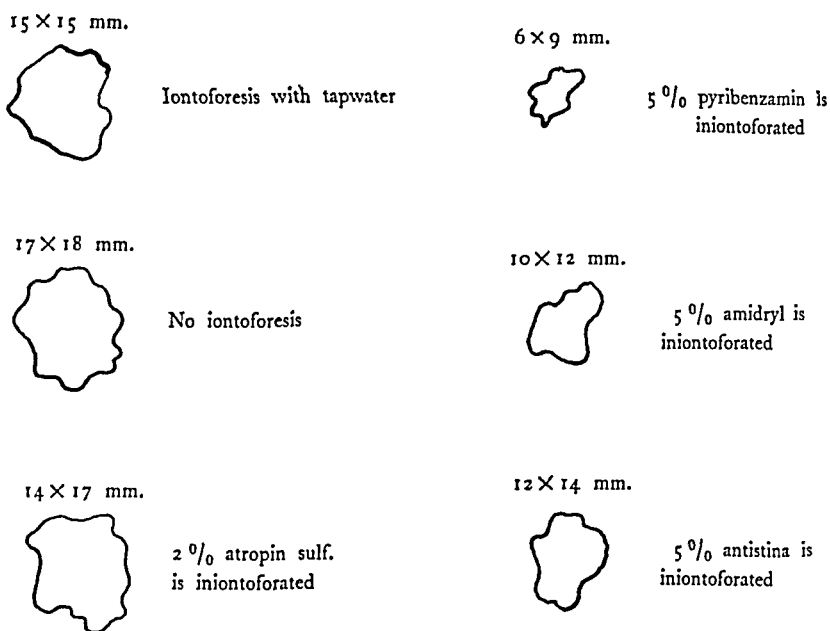


Fig. 7.

Prausnitz-Küstner reactions in skin areas with iontophoresis of antihistamines.

SUMMARY

Studies are reported on the effect of three antihistamines—antistina, amidryl and pyribenzamine—on the Prausnitz-Küstner reaction when these substances are 1) given per os in varying doses, 2) mixed with the allergen prior to its injection, and 3) introduced into the skin by iontophoresis, before the reactions are produced. On peroral administration, only pyribenzamine appears to have any effect. When they are mixed with the allergen prior to the injection, all three antihistamines inhibit the size of the papules. On employment of iontophoresis the three substances likewise appear to have some inhibitory effect.

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RECHERCHES SUR LA GENESE ET L'EVOLUTION DE LA NEPHRITE ALLERGIQUE EXPERIMEN- TALE ET INFLUENCE DES ANTIHISTAMI- NIQUES DE SYNTHESE SUR DE SYNDROME

PAR

B. N. HALPERN, I. TROLLET et J. MARTIN

INTRODUCTION

La question, si complexe encore, de la néphrite allergique expérimentale nécessite une revue succincte des principaux travaux auxquels elle a donné naissance depuis le début du siècle.

Ce bref aperçu — avant l'exposé de nos propres recherches — nous semble d'autant plus nécessaire que, si la plupart des auteurs décrivent une symptomatologie, une évolution et des lésions histologiques semblables, la pathogénie elle-même de la maladie reste encore obscure et donne lieu à nombre d'hypothèses.

Claude Bernard le premier avait déjà constaté qu'une injection de sérum provenant d'une espèce animale à un animal d'une autre espèce, déclenchait chez ce dernier une albuminurie plus ou moins durable.

Les premiers travaux, cependant, étudiant d'une façon plus systématique et plus approfondie la genèse et l'évolution de la néphrite expérimentale remontent à *Lindemann* (1). Au cours de ses recherches sur la toxicité de différents corps (poisons végétaux, animaux, vinylamine) sur le parenchyme rénal, il emploie du sérum de cobaye. Pour augmenter la toxicité de ce sérum, il injecte aux cobayes une émulsion de rein de lapin. Dans un second temps, il injecte le sérum ainsi préparé à des lapins et constate que les animaux traitées de la

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sorte présentent une albuminurie massive et meurent, en crise urémique, en trois à cinq jours. Des lapins témoins qui avaient reçu du sérum de cobaye normal ne présentaient pas de pareils symptômes. Il note en outre que la gravité des manifestations pathologiques était variable suivant les espèces animales choisies. Malheureusement, *Lindemann* n'a pas fait l'étude histologique des lésions.

A sa suite, *Schultze* (2) tente de reproduire ces expériences, mais n'y parvient pas. *Nefedieff* (3), lui, confirme les résultats de *Lindemann* en déclenchant cette fois des néphrites chez le cobaye. Il emploie également du sérum de lapins qui avaient reçu auparavant des injections répétées d'émulsion de rein de cobaye. Du point de vue anatomopathologique, il signale avant tout, des lésions vasculaires, tant au niveau des capillaires intra-glomérulaires qu'au niveau des vaisseaux afférents et efférents. Il démontre de plus qu'en liant un des uretères à un lapin, et qu'en injectant le sérum de cet animal 20 à 40 jours après l'intervention à un lapin sain, il déclenche chez ce dernier une albuminurie. L'examen histologique des reins révèle des lésions vasculaires semblables à celles qu'il avait rencontrées lors de l'expérience précédente.

Un grand nombre de travaux confirment ces expériences. Citons parmi eux, ceux de *Bierry* (4), *Castaigne* et *Rathery* (5), (6), (7), *Bierry*, *Petit* et *Schaeffer* (8), *Ascoli* et *Figari* (9), *Pearce* (10), *Pearce* et *Jackson* (11), *Lüdke* et *Schuller* (12), *Beebe* (13), *Sata* (14), etc.

Peu à peu, au cours des recherches, la notion de la « toxicité » des sérums suivant leur mode de préparation (hétéronéphrotoxines, isonéphrotoxines, auto-néphrotoxines), les espèces animales choisies, les doses injectées, se précisent.

De même, plusieurs auteurs établissent la spécificité très grande, sinon absolue, du sérum antirein, tant par des expériences *in vivo* qu'*in vitro* [(*Castaigne* et *Rathery* (6, 7)), *Woltmann* (15)] en particulier, dans une série de recherches sur les cytotoxines (néphrotoxines, hépatotoxines, spléno-toxines, endothéliotoxines) montre que la néphrotoxine est la plus spécifique de toutes sans cependant l'être absolument.

Durant cette phase des recherches, les investigations cliniques et de laboratoire se sont bornées au contrôle de l'albuminurie, parfois à l'examen du sédiment urinaire et de l'azotémie. En revanche, l'examen histologique des lésions a presque toujours été pratique. Il est frappant de constater que les auteurs, à l'exception de *Nefedieff*, signalent comme lésion primaire de la néphrite allergique l'atteinte des cellules épithéliales des tubes, qui sont pour la plupart en voie de dégénérescence. Ils négligent les lésions vasculaires qu'ils ont cependant tous mentionnés, mais qu'ils considèrent comme accessoires et secondaires.

Il faudra attendre une seconde série de chercheurs — citons en particulier les travaux de *Wilson* et *Oliver* (16) — pour montrer l'importance des lésions vasculaires, leur apparition primitive et précoce après l'injection de sérum antirein, et, plus tardivement l'apparition de lésions dégénératives des parois tubulaires.

C'est cependant avant tout aux importants travaux de *Masugi* (17, 18,

19) que nous devons, pour une bonne part, de nombreux éclaircissements et renseignements, tant sur la technique elle-même d'expérimentation, que sur la pathogénie, l'évolution clinique et l'histologie des lésions rénales. Il a démontré la très grande parenté du point de vue histologique, existant entre la néphrite expérimentale et la glomérulonéphrite aiguë de l'homme.

Masugi crée des néphrites chez le rat en lui injectant du sérum de lapin préparé antirein de rat. Il emploie pour l'immunisation des lapins la méthode de *Pearce* (20) et procède au dosage des anticorps contenus dans le sérum des lapins en mesurant le titre des précipitines.

Des contrôles anatomiques faits de 15 minutes à 14 jours après l'injection de sérum au rat permettent à *Masugi* de constater l'apparition des lésions déjà quelques heures après l'injection. Il distingue trois degrés dans le type des lésions, suivant le taux des anticorps dans le sérum et la quantité injectée.

1) 3 à 4 heures après l'injection, soit d'une dose minime d'un sérum fortement chargé en anticorps, soit d'une plus grande quantité d'un sérum faiblement chargé, *Masugi* note une hypertrophie et une hyperplasie des cellules endothéliales des capillaires glomérulaires et le remplissage de la lumière de ceux-ci par une masse albuminoïde homogène. Les capillaires sont dilatés et allongés par ce processus. Le nombre des érythrocytes est fortement diminué dans leur lumière.

Il constate aussi l'exsudation d'une substance albuminoïde des glomérules lésés dans la chambre capsulaire et même dans la lumière des canaux urinaires. Cette substance, dans les tubes, s'organise et prend l'aspect de cylindres hyalins.

Au bout de 24 h., le nombre des globules rouges diminue encore dans la lumière des capillaires tandis que la masse albuminoïde persiste et que la paroi des vaisseaux glomérulaires s'épaissit. Les épithéliums glomérulaires ne montrent pas de changements, à part un léger gonflement. Parfois, on constate un oedème discret, périvasculaire, au niveau des artérioles.

La différence essentielle entre ces lésions et celles que l'on rencontre dans la glomérulonéphrite aiguë chez l'homme réside dans le fait que tous les glomérules ne sont pas atteints dans la néphrite expérimentale.

2) Si l'on augmente la dose de sérum, on retrouve les mêmes lésions, mais il existe en plus une atteinte du parenchyme des tubes. La lumière des capillaires est fréquemment obstruée par une masse de fibrine qui s'organise en un thrombus et ne conserve pas son allure de substance albuminoïde homogène signalée plus haut. Le nombre des glomérules atteints est, là aussi, des plus variables. Ils sont nettement agrandis, et fréquemment, la chambre capsulaire est envahie par une substance albuminoïde. Les cylindres hyalins dans les canaux urinaires sont également beaucoup plus nombreux.

Après 24 à 48 heures, on note une hyperthrophie et une hyperplasie de l'épithélium glomérulaire. Les artères afférentes et les artères interlobulaires sont souvent remplies d'éléments provenant de la paroi vasculaire et l'on constate parfois une dégénérescence hyaline au niveau de la média.

Outre le gonflement des glomérules, l'épaississement des parois vasculaires

avec augmentation du volume de noyau des cellules endothéliales, un nouveau phénomène apparaît : le dépôt de la masse albuminoïde de la chambre capsulaire tend, dans certains cas, à s'organiser en se fixant d'une part à la paroi de la capsule, et d'autre part au peloton glomérulaire. Il en résulte la formation de l'image classique « en demi-lune ». On trouve également souvent des cylindres hyalins et des globules rouges dans les canaux urinaires et parfois il existe un léger oedème du tissu interstitiel. La présence de masses de fibrine traduirait une action plus violente du sérum toxique que celle de la substance albuminoïde homogène. Les lésions vasculaires sont plus importantes que dans le premier stade déjà décrit.

3) Le troisième degré dans le type des lésions constatées est dû à l'action d'un sérum très fortement chargé en anticorps. Au premier plan, on constate une stase marquée au niveau des capillaires intra-glomérulaires entraînant la nécrose des éléments cellulaires et souvent de fragments de noyaux appartenant vraisemblablement à des leucocytes lysés. Les noyaux de l'endothélium des parois présentent un aspect pycnotique. Les glomérules, très agrandis, compriment la partie initiale des tubes urinaires. En règle générale, les vaisseaux affectés, en revanche, sont fréquemment remplis d'érythrocytes. Les éléments cellulaires de la paroi des vaisseaux sont nécrotiques et prennent la coloration au Soudan.

Là encore, tous les glomérules ne sont pas atteints. Si les lésions évoluent pendant quelques jours, on constate toujours de la stase au niveau des vaisseaux glomérulaires, mais au niveau des artères, elle a disparu. On voit alors des lésions des parois avec infiltration sanguine intramurale. De nombreux vaisseaux sont thrombosés. Les canaux urinaires sont élargis, remplis d'une masse albuminoïde. Leur épithélium dégénéré, est aplati.

Si *Masugi* constate parfois au niveau du foie des lésions des capillaires fortement chargés en anticorps, il est très rare en revanche qu'un sérum antirénal très toxique provoque des lésions au niveau du rein. De nombreux contrôles *in vitro* Reprénant ces expériences, chez le lapin au moyen de sérum de canard chargé en anticorps antirénal, *Masugi* ne voit apparaître les signes cliniques de la néphrite (albuminurie, hématurie, cylindrurie, azotémie, hypertension) que 8 jours environ après l'injection du sérum, c'est à dire beaucoup plus tardivement que chez le rat (en moyenne 24 h.).

Les constatations histologiques faites sur le foie, le pancréas, la rate, le cœur, le poumon, les surrénales et les glandes sexuelles n'ont pas montré de lésions. Au niveau des reins, il retrouve les lésions déjà signalées, mais il note en plus que les glomérules para-corticaux sont plus souvent et plus gravement atteints que les autres, et que les lésions du troisième type (stase intracapillaire,

etc.) sont rares. L'exsudation de substance albuminoïde dans la chambre capsulaire et dans les tubes est, par contre, plus fréquente.

Les lésions du premier et du second degré peuvent guérir sans séquelles apparentes, mais on assiste parfois à une évolution vers la chronicité, avec formation d'images en demi-lune, dégénérescence hyaline des capillaires glomérulaires et prolifération des épithéliums de la capsule. Ces lésions peuvent aller jusqu'à la transformation des glomérules en boules hyalines.

La morphologie des lésions vasculaires est comparable en tous points à celle rencontrée dans l'anaphylaxie locale et l'inflammation hyperergique décrite par *Rossle* (21).

Masugi fait donc de la néphrite expérimentale une manifestation allergique avant toute chose.

Nous verrons par la suite que, si la majorité des auteurs qui ont étudié la question considèrent bien la néphrite expérimentale comme une manifestation allergique, il semble toutefois, que le problème soit plus complexe, et qu'il ne s'agisse pas uniquement d'une action antigène-anticorps.

Les nombreux travaux entrepris depuis ceux de *Masugi* ont tous confirmé les résultats de ce dernier et mis au premier plan les lésions vasculaires des capillaires glomérulaires avec hyperhémie et exsudation intraglomérulaire. Secondairement, apparaissent les lésions de dégénérescence cellulaire des tubes.

Citons parmi les travaux les plus importants : *Hemprich* (22), *Weiss* (23), *Arnott, Kellar et Matthews* (24), *Koranyi et Hamori* (25), *Smadel* (26, 27), *Smadel et Farr* (28), *Tsujii* (29), *Ehrich, Wolf, Bartol* (30), *Kay* (31), *Rathery* (32).

Pour *Smadel* cependant, la présence d'une hématurie n'est pas un des caractères de la néphrite allergique expérimentale. La lésion spécifique de la néphrite allergique serait avant tout, pour lui, une dégénérescence tubulaire de type hyalin. Suivant la pureté des anticorps antirein dans le sérum, il obtient des lésions plus ou moins spécifiques, mais, l'hyperhémie glomérulaire, les lésions vasculaires, l'hématurie, incomberaient aux autres anticorps contenus dans le sérum du fait de la variété des tissus qui composent le rein. Cette hypothèse avait déjà été soutenue par *Pearce* (10) en 1903.

Ainsi s'expliquerait pour *Smadel*, cette sorte de réaction anaphylactoïde que font parfois les animaux lors de l'injection du sérum. Avec un sérum suffisamment pur, il n'a jamais constaté d'hématurie, même si ce dernier était très riche en anticorps, quelles que fussent les doses injectées. Cependant, si les capillaires glomérulaires ne présentaient pas de lésions lors des contrôles histologiques, il a toutefois remarqué, à côté de la dégénérescence hyaline des tubes, un agrandissement des glomérules qui étaient comblés d'une matière albuminoïde. Dans les cas évoluant vers la chronicité, il note, comme les autres auteurs, une prolifération des cellules de la capsule de Bowmann, allant jusqu'à la sclérose glomérulaire, ainsi que des lésions de dégénérescence et de sclérose des parois vasculaires.

Citons en passant qu'avec *Swift, Smadel* (33), est parvenu à protéger le

rat contre l'action du sérum antirein, en injectant préventivement un extrait salin de rein de rat. Une injection de sérum physiologique seule ou d'extrait salin de foie de rat n'a, en revanche, aucun effet protecteur.

Les travaux entrepris, depuis 1939 environ, cherchent de plus en plus à mettre en évidence le côté allergique de la néphrite expérimentale.

Sarre et Wirtz (34) montrent, que si l'on parle de sérum « néphrotoxique », il ne faut pas prendre le terme de « toxines » dans son sens habituel, mais qu'il s'agit bien d'anticorps qui réagissent avec le rein, jouant le rôle d'antigène, et que la néphrite expérimentale est une manifestation allergique avant toute chose.

Pour le prouver, ils extériorisent un rein de lapin et posent une pince sur l'artère rénale quelques minutes avant l'injection de sérum toxique. Ils laissent la pince en place 15 minutes après l'injection. L'animal fait une néphrite du type décrit par *Masugi*, mais lors du contrôle histologique *Sarre et Wirtz* constatent, que si le rein dont la circulation n'a pas été interrompue présente les lésions habituelles de la néphrite expérimentale, l'autre rein, ne présente pas de lésions, ou fort peu, suivant la richesse en anticorps du sérum injecté. Ils fournissent ainsi la preuve de la rapide fixation des anticorps (15 minutes) sur le rein.

Si dans la première phase des recherches plusieurs auteurs, en particulier *Castaigne et Rathery*, ont montré la présence d'autonéphrotoxines — ou pour employer une terminologie plus récente d'auto-anticorps — créés par l'injection intra-péritonéale d'une émulsion de rein de lapin à un lapin, et s'ils ont montré la néphrotoxicité acquise par ce sérum, ce n'est qu'en 1939 que *Schwentker et Comptoier* (35) reprennent en détail la question et montrent clairement la possibilité de la création d'auto-anticorps en employant la technique suivante : ils injectent dans le péritoine de lapins normaux une émulsion de rein de lapin additionnée soit de toxine streptococcique, soit staphylococcique, vu la grande résistance du lapin envers la streptotoxine. Ces injections sont répétées 10 fois, tous les deux jours. Après l'immunisation, ils dosent dans le sang du lapin, par une méthode de déviation du complément, en employant une émulsion de rein de lapin comme antigène — le taux des anticorps. La réaction est positive jusqu'à une dilution de $\frac{1}{50}$ du sérum de lapin.

Dans une autre série d'essais, ces auteurs montrent, par une méthode d'adsorption des anticorps *in vitro*, que le sérum antirein contient au moins deux sortes d'anticorps, l'une spécifiquement antirein, l'autre se fixant sur d'autres organes (cerveau par exemple), du fait de la variété des tissus qui composent le rein et qui, par la méthode même de la préparation de l'émulsion, se trouvent mêlés au parenchyme rénal. Ils décelèrent également la présence d'anticorps antirein dans le sérum des scarlatineux, que ceux-ci fassent ou non une néphrite.

Reprenant les travaux de *Schwentker et Comptoier*, *Cavelti* (36, 37) par une technique similaire démontre, non seulement la présence d'auto-anticorps *in vitro* par une méthode mise au point par lui en 1944 (38), mais encore

que ces auto-anticorps sont capables de déclencher une néphrite chez les rats. Suivant le mode d'immunisation des animaux, il provoque soit des lésions de glomérulonéphrite typique, telles que les a décrites *Masugi*, soit des lésions frappant essentiellement les tubuli. L'évolution clinique est elle-même différente : dans le premier cas *Cavelli* constate l'existence d'albuminurie, de cylindrurie, et d'hématurie, alors que dans le second type, il n'y a que peu ou pas d'albumine dans les urines, et la présence de cylindres et de sang est rare. Dans les deux cas, il existe une période de latence entre l'injection et l'apparition des premiers signes cliniques de néphrite, variant de 8—10 jours à 2—3 semaines. Les expériences témoins consistant à injecter soit un extrait rénal seul, soit de la streptotoxine seule, n'ont pas permis de déceler d'auto-anticorps dans le sérum des rats. Seules, des injections massives de streptotoxine ont parfois suscité l'apparition d'anticorps dans le sérum.

Chez le lapin, *Cavelli*, n'est parvenu qu'à de rares exceptions près à provoquer une néphrite par un procédé semblable, bien que le sérum de ces animaux ait un taux d'anticorps élevé.

Kay (39, 40), *Kay*, *Luchesi* et *Rutherford* (41) reprennent les expériences de *Masugi*, en employant la même méthode que ce dernier. Les animaux développent une néphrite en tous points superposable à celle décrite par *Masugi*, tant au point de vue clinique qu'histologique.

En cherchant à hâter l'apparition des symptômes cliniques ou au contraire à entraver l'évolution de la néphrite au moyen des rayons X, ils donnent une explication un peu différente de celle de *Masugi* sur la pathogénie de la maladie.

Nous y reviendrons dans la suite, lors de la discussion du mécanisme de la néphrite allergique expérimentale.

Fouts, *Corcoran* et *Page* (42) à leur tour provoquent des néphrites chez le chien en lui injectant du sérum de poule préparé antirein de chien. Ils font, à quelques différences près, les mêmes constatations que les autres auteurs : albuminurie, hématurie, cylindrurie, taux exagérément élevé de l'urée sanguine. La pression artérielle, elle, ne varie pratiquement pas. Ils prouvent l'atteinte de la fonction rénale par de nombreux tests (augmentation du débit sanguin rénal, diminution du pouvoir de filtration glomérulaire, etc.). Anatomopathologiquement, ils constatent également une hyperhémie des glomérules, qui sont agrandis, remplis de substance hyaline et une dégénérescence secondaire des tubes.

Reubi (43) enfin, en 1946, reprend les expériences de *Masugi* et pensant que la néphrite expérimentale était dûe, lors de la copulation anticorps-antigène au niveau du rein, à la libération d'histamine ou de substances histaminiques liées à une protide de la cellule rénale, tente de protéger l'animal en lui donnant un antihistaminique de synthèse (*Antistine*).

A l'appui de sa théorie, il trouve une élévation du taux d'histaminase dans le parenchyme rénal à la fin du temps de latence entre l'injection de sérum et l'apparition des signes cliniques de néphrite, alors que le taux d'histamine

ne varie pas sensiblement. Il en conclut qu'il se détruit plus d'histamine dans l'organisme pendant le développement de la néphrite qu'à l'état normal et par conséquent, puisque le taux reste inchangé, il doit s'en former davantage. Histologiquement, les animaux présentent des lésions du même type que celles décrites par *Masugi* : nombre plus ou moins important de glomérules atteints, espaces capsulaires distendus par un exsudat albumineux, prolifération endothéliale des vaisseaux, formation d'images en demi-lune, stéatose des tubes, parfois atrophie. Dans les cas les plus graves, il note une dégénérescence hyaline des glomérules et une atrophie plus marquée des tubes.

Les animaux traités par l'Antistine ont une évolution très différente, suivant l'application préventive ou curative de la thérapeutique : a) — les animaux traités préventivement, et d'une façon ininterrompue durant la maladie présentent des signes cliniques beaucoup plus discrets et le rein est histologiquement normal ; b) — les animaux qui n'ont reçu qu'une protection préventive, mais non durant le développement de la maladie, présentent des lésions rénales atténuées ; c) — les animaux ayant reçu l'antihistaminique au moment de l'apparition des premiers symptômes cliniques (albuminurie) font des lésions plus marquées, mais cependant de moindre importance que les animaux témoins ; d) — les animaux traités 4 à 5 jours après l'apparition des signes cliniques présentent des lésions d'intensité presque semblable à celle des animaux témoins ; e) — au stade subchronique, l'antihistaminique ne semble pratiquement pas avoir d'effet sur l'évolution de la maladie.

Donc, le traitement précoce et préventif seulement paraît avoir une heureuse influence sur l'évolution de la néphrite.

Signalons, dans un même ordre d'idées, lors des recherches de l'effet des antihistaminiques de synthèse sur les lésions de myocardite provoquées par l'injection de sérum de cheval à des lapins, selon la technique de *Rich* et *Gregory* (44) — lésions simulant absolument la myocardite rhumatismale —, *Kyser, McCaster* et *Stengle* (45) ont constaté que l'injection préventive d'un antihistaminique de synthèse (Bénadryl) protégeait les animaux d'une façon efficace.

Pour terminer, nous mentionnerons l'important travail d'*Ahlström* (46) tendant, une fois de plus, à établir la nature allergique de la néphrite expérimentale. Cet auteur a employé une méthode différente de celles utilisées jusqu'ici. Dans un premier groupes d'expériences, il injecte de la streptotoxine dans l'artère rénale du lapin et ne constate que peu ou pas de lésions au niveau du rein, dans un laps de temps s'étendant entre 8 heures et 10 jours après l'injection. Après sensibilisation de l'animal à la toxine de *Dick*, l'action de la streptotoxine n'est guère plus marquée sur le rein.

En injectant d'autre part du sérum de cheval dans l'artère rénale du lapin, il ne note aucune lésions rénale. Même après sensibilisation de l'animal au sérum de cheval, les lésions sont peu marquées. Mais, en répétant, chez des animaux sensibilisés, l'injection intra-rénale de sérum de cheval, il constate alors une nette atteinte des glomérules qui préhendent une image semblable

à celle décrite par *Masugi*. Dans un troisième groupe d'expériences, *Ahlström* emploie, cette fois, de la staphylotoxine. Chez l'animal normal, suivant la dose injectée dans l'artère rénale, il provoque des lésions nécrotiques, plus ou moins étendues, frappant particulièrement les endothéliums vasculaires. Mais pour obtenir ces lésions, il faut employer des doses de staphylotoxine mortelles dans les 24 à 48 h. Avec des doses inférieures, il n'obtient que peu ou pas de lésions. Si, en revanche, il injecte au lapin des doses non mortelles, de staphylotoxine, après l'avoir sensibilisé au sérum de cheval, il constate suivant la dose de staphylotoxine injectée, des lésions d'intensité variable rappelant d'une manière frappante les divers types de lésions décrites par *Masugi*. Les examens de contrôle au niveau des autres organes révèlent dans le foie de fréquentes nécroses, intéressant particulièrement les acini, les espaces portes et les capillaires hépatiques. Les poumons présentent eux, une prolifération de l'intima des artères. Au niveau du cœur, on note la dégénérescence des fibres musculaires et des lésions rappelant les nodules d'Aschoff.

La création de lésions rénales avec d'autres toxines et poisons (toxines diphtériques, venin de cobra, nitrate d'urane), n'a pratiquement jamais été couronnée de succès, que l'on agisse sur des animaux sensibilisés ou non. Seule, la toxine de *Dick* a une action sur le foie des animaux sensibilisés.

Il ressort de ce travail que la nature allergique de la maladie est certaine, même si d'autres facteurs entrent en ligne de compte (facteur toxique). À l'appui de sa théorie, *Ahlström* retient les faits suivants : 1) par leurs caractères, les lésions se distinguent nettement de celle produites par une toxine seule (staphylotoxine). 2) les lésions en rappellent d'autres produites par des méthodes différentes, mais où le facteur allergique intervient certainement (néphrites de *Masugi*). 3) avec les mêmes doses de toxines, les lésions rénales sont beaucoup moins accusées chez les animaux qui n'ont reçu qu'une petite dose de sérum sensibilisant que chez ceux qui en ont reçu une plus forte. 4) chez les animaux traités avec de la staphylotoxine et sensibilisés au sérum de cheval, on obtient encore des lésions très appréciables avec une dose de staphylotoxine trop faible pour déclencher, employée seule, des lésions sur un animal témoin.

La localisation essentiellement rénale des lésions doit tenir au fait de la sensibilisation préalable du rein par la staphylotoxine ; si l'on rencontre cependant des lésions au niveau d'autres organes, (foie particulièrement) cela prouve l'affinité particulière de la staphylotoxine pour l'endothélium des capillaires.

Il nous a semblé intéressant de reprendre, une fois encore, les expériences de *Masugi* à la lumière des résultats antérieurs et en étudiant à la fois les données immunologiques, la biochimie et l'anatomie pathologique des néphrites expérimentales.

Nous avons également repris l'étude de l'action des anti-

histaminiques de synthèse sur l'évolution de la maladie. Cette question a un grand intérêt thérapeutique et méritait d'être approfondie.

RECHERCHES PERSONELLES

A). TECHNIQUES EMPLOYEES

1) *Immunisation des canards :*

Nous avons employé comme donneur de sérum des canards de Barbarie (*Cairina Moschata*). Ces derniers ont reçu, par voie intra-péritonéale, selon la technique décrite par Masugi (18), 20 à 24 injections de 10 cc. chacune d'une émulsion de rein de lapin. Les injections étaient espacées de 5 à 7 jours.

La préparation de l'émulsion de rein a été faite de la manière suivante :

Le lapin est saigné à blanc, par section de la carotide. Après ouverture de l'abdomen, on ligature l'aorte en amont de l'embranchement des artères rénales, et à environ 3 cm au dessous de cet embranchement. Les collatérales issues de l'aorte et des artères rénales sont également ligaturées. On introduit alors une canule dans l'aorte abdominale entre les deux ligatures. Les veines rénales, dégagées, sont sectionnées. On perfuse les reins avec 5 litres de solution de Cl Na à 9 pour mille, pour les débarrasser complètement du sang qu'ils contiennent. Les reins sont prélevés et broés dans un mortier avec du sable fin de Fontainebleau lavé et environ 20 cc. de solution de Cl Na à 9 pour mille. On broie jusqu'à l'obtention d'une bouillie homogène. On filtre sur gaze et l'on centrifuge le filtrat 3 minutes à 2500 tours/minute. On ajoute alors la quantité nécessaire de solution de Cl Na à 9 pour mille pour obtenir 60 à 70 cc. de liquide.

Huit jours environ après la dernière injection d'émulsion de rein, les canards sont saignés. Le sang est recueilli aseptiquement par une canule placée dans la veine jugulaire. Après centrifugation, le sérum est conservé à la glacière jusqu'au moment de son emploi. Nous avons renoncé à inactiver le sérum par chauffage à 56° pendant une demi-heure, craignant de l'altérer par ce procédé.

2) *Contrôle sérologique :*

Nous avons dosé, pour chacun des 6 canards immunisés le taux des anticorps contenus dans le sérum.

Ces dosages ont été faits suivant la technique de *Kolmer* (6, 47).

Si nous avons choisi cette méthode, c'est parce que parmi les réactions de fixation du complément, la réaction de *Kolmer* se trouve être jusqu'à maintenant la plus sensible parmi les techniques similaires. D'une part, en effet, *Kolmer* emploie de très faibles quantités de globules rouges et de complément, si bien que le rapport sérum hémolytique/complément qui conditionne la sensibilité de la réaction est optimum. D'autre part, le titrage préalable du sérum hémolytique et du complément du jour assure la constance de la réaction.

La réaction se fait sur le schéma suivant¹ :

Tube-réaction : T.R.			
Tube-témoin-sérum : T.T.S.		T.R. ²	T.T.S.
Sérum de canard		I	I
Antigène dilué au ¼		III	
Eau salée à 0,85 %			III
Complément titré contenant 2 full units ³ par cc		0,3	0,3
15 à 18 heures à la glacière, dans la partie la moins froide, plus 15 min. à 37° au bain-marie.			
Sérum hémolytique titré à 2 unités ⁴ , dans 0,5 cc		III	III
Globules rouges à 2 %		III	III
1 Heure à 37° au bain-marie.			

Le tube témoin-sérum doit montrer une hémolyse totale, sinon le sérum est anti-complémentaire. Pour chaque série de réaction, on dispose en outre de :

- un tube témoin-antigène, (pas de sérum)
- un tube témoin-système hémolytique (ni sérum ni antigène)
- un tube témoin-globules rouges (eau salée et GIR.)

Les 2 premiers tubes doivent présenter une hémolyse totale, et le troisième une hémolyse nulle.

¹ Tiré du travail de *R. Laporte*.

² Les chiffres romains désignent les gouttes de la pipette Duclaux donnant XX gouttes au cc.

³ Une « full unit » est la dose immédiatement supérieure à l'unité réelle du complément, celle-ci étant égale à la dose minima réalisant l'équilibre du système hémolytique (une « full unit » = une unité + 0,05).

⁴ Une unité hémolytique = dose minima de S.H. donnant une hémolyse totale.

* Nous tenons à remercier 6 Dr. Laporte de l'Institut Pasteur de Paris, de son obligeance et de ses précieux conseils.

Notation des résultats :

Si l'hémolyse est totale (100 %)	—
„ „ „ importante (75 %)	+
„ „ „ „ (50 %)	++
„ „ „ faible (25 %)	+++
„ „ „ nulle	++++

RESULTATS OBTENUS

Sérum du canard I	++
„ „ „ II	++++
„ „ „ III	++++
„ „ „ IV	++++
„ „ „ V	+++
„ „ „ VI	++++

Le dosage quantitatif se fait suivant le schéma suivant
(1) :

	T. R. ₁	T. R. ₂	T. R. _x	T. T. S. ²
Sérum dilué	0,5	0,5	0,5	1 ¹
Antigène dilué à 1/4	0,5	0,5	0,5	
Complément (2 full unit/cc.)	1	1	1	1

Fixation 15 à 18 heures, entre 6 et 8° C.,
plus 10 m. à 37° bain-marie.

Sérum hémolytique (2 unités)	0,5	0,5	0,5	0,5
Globules rouges à 2 %	0,5	0,5	0,5	0,5

1 heure à 37° au bain-marie.

	Dilution du sérum							Résultats
	1/2	1/4	1/8	1/16	1/32	1/64	1/128	
Sérum du canard 1	+	—	—	—	—	—	—	+ 1/2
„ „ „ 2	+	+	+	—	—	—	—	+ 1/8
„ „ „ 3	+	+	+	+	—	—	—	+ 1/16
„ „ „ 4	+	+	+	—	—	—	—	+ 1/8
„ „ „ 5	+	+	—	—	—	—	—	+ 1/4
„ „ „ 6	+	+	+	+	+	+	—	+ 1/64

Les résultats indiquent la ruie dilution ou l'hémolyse était nulle.

Nous avons employé comme antigène l'émulsion de rein préparée selon la technique habituelle et diluée au 1/4.

¹ Tiré du travail de R. Laporte.

² Le T.T.S. contient du sérum non dilué.

Nous insistons sur l'importance de pratiquer le dosage des anticorps, car si tous les canards ont été immunisés de la même façon, le taux des anticorps est, suivant l'animal, des plus variables.

L'évolution et la gravité de la néphrite étant conditionnées avant tout par le taux des anticorps, nous avons répartis les animaux en 4 lots :

1° : Lapins injectés avec un sérum très riche en anticorps (canard 6).

2° : lapins injectés avec un sérum moyennement chargé en anticorps (canard 3).

3° : lapins injectés avec un sérum pauvre en anticorps¹. (canards 2 et 4).

4° : lapins injectés avec du sérum normal de canard (témoins).

3) *Choix et contrôle des lapins :*

Nous avons choisi des lapins pesant en moyenne 2 kg. Les animaux ont été suivis pëndant 3 à 8 jours avant l'injection de sérum. Durant cette période, nous avons contrôlé le poids, la pression artérielle (mesurée au niveau de l'artère centarle de l'oreille par une methode noin sanglante de *Grant* et *Rothschild*), la quantité d'urine en 24 heures, le poids spécifique de celle-ci, l'albumine, le sédiment urinaire et l'azotémie.

Ces examens ont été répétés, les uns quotidiennement, les autres tous les 8 à 10 jours, durant une période de 1 mois à 50 jours après l'injection du sérum. Des examens de contrôle ont été pratiqués de temps à autre chez les survivants qui ont été sacrifiés après 6 à 7 mois.

En cours d'expérience, plusieurs animaux de chaque lot ont subi des biopsies rénâles qui ont été répétées chez plusieurs d'entre eux. L'examen histologique des reins a été fait systé-

¹ Dans cette expérience, nous avons employé le sérum de 2 canards ayant le même taux d'anticorps, car les lapins ont subi une seconde injection de sérum 15 jours après la première.

matiquement. Le foie des animaux a été également examiné dans la majorité des cas.

Nous avons choisi comme antihistaminique de synthèse le Phenergan (3277 R. P.) (N-diméthylamino-2-propyl-1-thio-diphénylamine), dont les propriétés et l'action ont été étudiées en détail par *Halpern* (53).

B) RESULTATS

Dans l'exposé qui va suivre nous allons rapporter les faits expérimentaux dans l'ordre suivant : tout d'abord nous allons donner une définition des termes dont nous allons nous servir pour interpréter les images anatomopathologiques. Nous exposerons ensuite les 38 expériences classées en 4 grands groupes, suivant la gravité du syndrome : 1) néphrite suraigüe ; 2) néphrite aigüe ; 3) néphrite subaigüe ; 4) le 4ème lot étant le lot témoin. Dans le cadre de chaque groupe nous relaterons les expériences individuelles et nous condenserons sous forme d'un résumé les faits essentiels qui caractérisent chacun de ces groupes d'essais.

Remarques préliminaire. Définition des termes :

Pour la compréhensions des termes par lesquels nous désignons la gamme des lésions histologiques du rein il nous paru indispensable de définir les divers termes pour nous allons nous servir plus loin¹.

Ces lésions ont été observées sur les glomérules et les tubes.

a) LÉSIONS GLOMÉLAIRES

1) *Intumescence* : Nous appelons « *intumescence* », un état particulier de la paroi des anses capillaires du floculus qui se traduit par leur épaissement. Cet épaissement

¹ Nous remercions vivement Monsieur le Professeur *Oberling*, prof. a la Faculté de Médecine de Paris qui a bien voulu nous aider de ses conseils au cours de ce travail.

est plus ou moins dense et donne l'impression d'une imbibition oédémateuse qui ne modifie pas l'architecture du floculus. Elle ne prend pas les colorants du collagène et ne s'accompagne pas en général d'altération des éléments de l'anse. Elle donne parfois un aspect « lavé » au floculus. (Planche I)

2) *Congestion* : Nous désignons sous ce terme la présence en nombre supérieur à la normale, d'hématies dans la lumière des capillaires du floculus. La congestion des glomérules s'étend parfois, aussi bien aux glomérules sous-capsulaires, qu'aux glomérules juxta-médullaires. Mais, assez souvent, elle n'intéresse que les glomérules sous-capsulaires.

3) *Anémie glomérulaire* : Nous entendons par là l'absence d'hématies dans les capillaires du floculus. L'anémie glomérulaire marche souvent de pair avec le collapsus des capillaires. Cependant, elle peut se voir fréquemment associée à une dilatation des anses qui sont ainsi béantes, mais vides. L'anémie glomérulaire est une manifestation très souvent rencontrée, elle marche souvent de pair avec l'intumescence des floculi.

4) *Prolifération endothéliale* : Cette prolifération consiste en une hyperplasie des cellules endothéliales tapissant la paroi des anses du côté de la lumière vasculaire. Elle aboutit à une densification plus ou moins importante du floculus en rapport avec une augmentation souvent considérable du nombre de noyaux de ces cellules. Il s'agit là d'une modification très souvent constatée sur les lames étudiées. (Planche II)

5) *Sclérose* : Dans quelques cas, nous avons constaté un début de remaniement scléreux de la trame interstitielle du floculus. Quelquefois, ce début de sclérose interstitielle s'accompagne d'un épaississement fibreux plus ou moins accusé de la capsule de Bowmann (Planche III). Dans quelques cas, qui restent tout à fait exceptionnels, nous avons pu constater quelques glomérules complètement fibrosés et transformés par un processus de sclérose centrifuge en « pain à cacheter ».

6) *La présence de substance albuminoïde dans la lumière capsulaire* est constatée sur un très grand nombre de nos pré-

parations. A notre avis, la nature albuminoïde de cette substance peut être affirmée sur son aspect amorphe, homogène, uni et monochrome (Planche IV).

7) *La présence de débris dans la lumière capsulaire* est un fait d'observation fréquente. Ils se présentent soit sous un aspect grenu, soit sous forme d'un très fin réseau. Ils sont franchement éosinophiles et leur nombre est très variable (Planche V). La nature exacte de ces débris ne peut être affirmée. Il ne s'agit certainement pas de débris hématiques, ni vraisemblablement de débris cellulaires. Il est probable par contre qu'il s'agisse de la même substance que la substance albuminoïde, son aspect différent étant sans doute en rapport avec un état physicochimique différent.

b) LÉSIONS TUBULAIRES

Sous ce terme nous entendons, soit des altérations intéressant le revêtement épithélial du tube, soit simplement la présence dans la lumière des tubes de cylindres dont la nature n'a pas pu toujours être identifiée.

1) *Lésions épithéliales* : Les lésions se présentent sous deux aspects différents : tantôt, il s'agit de dégénérescence ou de nécrose cellulaire avec pycnose nucléaire (Planche VI), suivie de desquamation de la cellule, tantôt il s'agit de dégénérescence graisseuse (Planche VII). Dans certains cas, les lésions épithéliales ne sont point apparentes, mais la constatation de cellules de revêtement prenant un aspect plasmodial permet d'affirmer qu'il y a eu altération et desquamation de l'épithélium et que celui-ci est en voie de régénération.

2) *La présence de cylindres dans la lumière des tubes* est un fait d'observation courante. Tantôt, il s'agit de cylindres hyalins, constitués par la même substance que la substance albuminoïde mise en évidence dans la lumière capsulaire des glomérules (Planche VIII). Tantôt, il s'agit de cylindres granuleux. Ceux-ci sont de plusieurs natures : ce peuvent être des cylindres constituées de débris comparables à ceux mis en évidence dans la lumière capsulaire des glomérules ou de

débris épithéliaux nécrosés (Planche IX). Ce peuvent être des cylindres constitués d'hématies en voie de lyse ou enfin des cylindres formés d'amas nécrotiques de nature indéfinissable (Planche X).

Note importante : Un caractère commun relie toutes ces modifications morphologiques et demande à être souligné d'emblée : c'est leur topographie toujours segmentaire. Les seules variations dépendent de l'étendue des zones où l'atteinte se manifeste. Cette topographie segmentaire est particulièrement évidente lorsqu'il s'agit de lésions des tubes.

I. NEPHRITES SURAIGUES

(Lapins ayant reçu, par voie intra-veineuse, 8 cc. de sérum du canard n° 6 ;)

Le premier lot de lapins comprend 10 animaux, dont 5 ont été traités par l'antihistaminique de synthèse (3277 R. P.), à raison de 10 mgr./Kg, en injection sous-cutanée, une heure avant l'injection de sérum. Cette dose a été répétée quotidiennement pendant la durée de l'expérience.

Les graphiques ci-dessous nous montrent l'évolution de la maladie :

- a) chez les animaux témoins,
- b) chez les animaux traités.

Nous donnerons à la suite de chaque graphique les renseignements cliniques complémentaires ainsi que le compte-rendu anatomo-pathologique pour chaque animal.

A. ANIMAUX TÉMOINS

Lapin N° 986 (fig. N° 1).

Evolution : L'animal a présenté, quelques minutes après l'injection de sérum de canard des symptômes de choc (agitation, tachycardie, polypnée, chute de la pression artérielle) ; ces symptômes ont disparu après 10 à 15 minutes. 48 heures après l'injection, l'animal est mort. Durant ce laps de temps, il a présenté une oligurie avec augmentation notable du poids spécifique urinaire, une albuminurie et une hématurie macroscopique, mais pas de cylindrurie. L'azotémie, de 0,45 gr/

gr/mille. Les modifications tensionnelles et urinaires sont schématisées par le graphique No. 1.

Autopsie : Rein gauche : 7,5 gr.

Rein droit : 7,9 gr.

Les reins sont oedématisés, gorgés de sang, de couleur rouge foncée. Les autres organes ne présentent pas d'altérations macroscopiquement décelables.

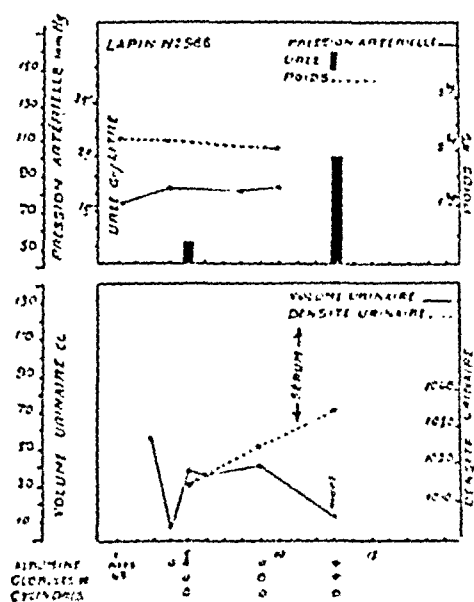


Figure 1.

Histologie : Très forte intumescence de tous les flocculus associée à une prolifération très notable des cellules endothéliales. On note, avec une fréquence égale, la présence en grande abondance de substance albuminoïde ou de nombreux débris dans la lumière capsulaire. Les anses flocculaires sont pratiquement vides d'hématies.

En quelques points de la préparation, il existe des lésions épithéliales segmentaires. Ces lésions sont caractérisées soit par des phénomènes dégénératifs, allant jusqu'à la nécrose, soit par des phénomènes de réparation dont témoigne la présence de plasmodes. Presque tous les tubes contiennent dans leur lumière des cylindres, ceux-ci sont quelquefois des cylindres hyalins, plus souvent, ce sont des cylindres granuleux faits de débris ou d'éléments épithéliaux dégénérés et desquamés. Dans quelques cas, ces cylindres granuleux sont constitués par des hématies en voie de lyse. De tels cylindres sont nettement plus abondants au niveau des tubes de la corticale qu'au niveau de ceux de la médullaire.

Lapin N° 985 (fig. N° 2).

Evolution : Superposable en tous points à celle du lapin n° 986. Mort 48 heures après l'injection de sérum. L'azotémie a passé de 0,36 gr/litre à 2,62 gr/litre.

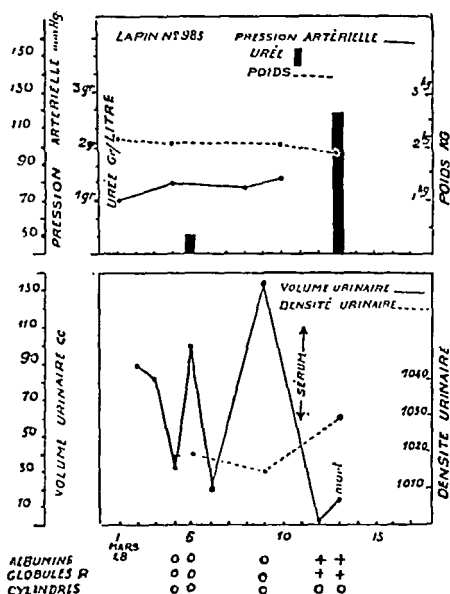


Figure 2.

Autopsie : Rein gauche : 10,3 gr.

Rein droit : 11,2 gr.

Les reins présentent à un degré encore plus accentué les caractères décrits pour ceux du lapin n° 986.

Histologie : Tous les floculus sont fortement intumescents. Ces phénomènes s'accompagnent le plus souvent d'une prolifération endothéliale notable. Dans la lumière capsulaire, on constate très souvent la présence de débris et quelquefois celle de substance albuminoïde. La présence d'hématies dans les anses capillaires est exceptionnelle.

En d'assez nombreuses régions, on peut constater l'existence de lésions épithéliales segmentaires, il s'agit de lésions dégénératives pouvant aller jusqu'à la nécrose. En quelques points, on constate des phénomènes de régénération épithéliale caractérisée par l'aspect plasmodial ou indifférencié des cellules qui revêtent le tube. Pratiquement tous les tubes contiennent des cylindres. Ceux-ci sont soit des cylindres hyalins, soit des cylindres constituées de débris ou d'éléments épithéliaux nécrosés ou desquamés. En outre, on constate l'existence de cylindres constitués d'hématies en voie de lyse.

Lapin N° 991 (fig. N° 3).

Evolution : Identique aux deux cas précédents. La mort est survenue en 48 heures. L'azotémie passe de 0,42 gr/litre à 1,61 gr/litre.

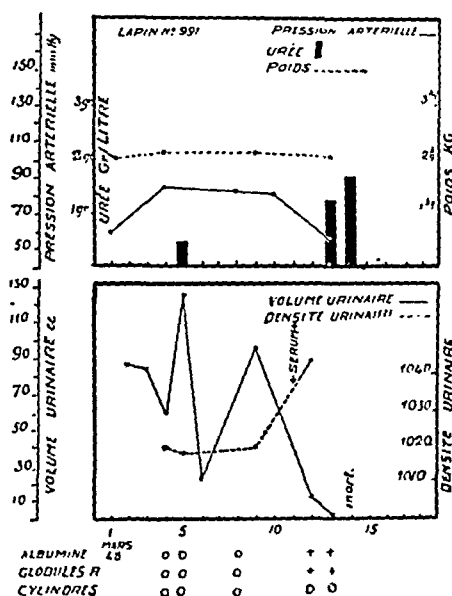


Figure 3.

Autopsie : Rein gauche : 9,7 gr.

Rein droit : 11,1 gr.

Ils présentent les mêmes caractères que ceux des lapins 985 et 986.

Histologie : Très forte intumescence des floculus associée à une prolifération endothéliale plus ou moins remarquable suivant les glomérules considérés. Présence dans la lumière capsulaire de quelques glomérules soit de substance albuminoïde, soit le plus souvent de débris. Absence quasi complète d'hématies dans les anses floculaires.

Dans certaines régions on constate des lésions épithéliales segmentaires. Ces lésions sont caractérisées par des phénomènes dégénératifs allant jusqu'à la nécrose. Les tubes présentent pratiquement tous des cylindres dans leur lumière. Ces cylindres sont soit hyalins, soit granuleux. Ces derniers sont constitués soit par des débris, soit par des éléments épithéliaux nécrosés et desquamés. Dans certains cas, ces cylindres sont constitués par des hématies en voie de lyse. De tels cylindres se retrouvent avec les mêmes aspects aussi bien dans les tubes de la médullaire que dans ceux de la corticale.

Lapin N° 500 (fig. N° 4).

Evolution : Semblable à celle des animaux précédents. La mort survient après 48 heures. L'azotémie passe de 0,30 gr pour mille à 1,59 gr pour mille.

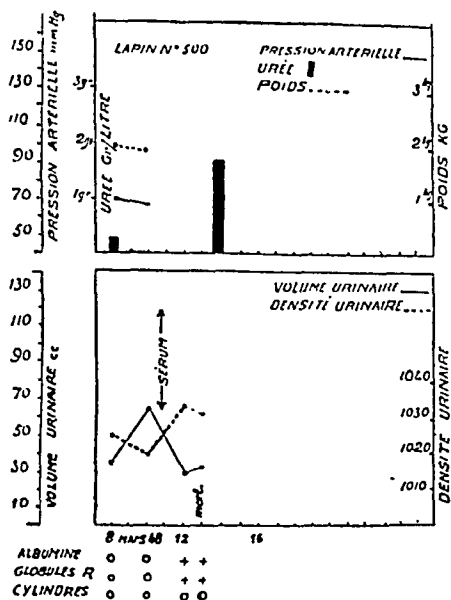


Figure 4.

Autopsie : Rein gauche : 9,2 gr.

Rein droit : 8,5 gr.

Aspect identique aux reins précédents.

Histologie : Les floculus sont tous très fortement intumescents. A cette intumescence s'associe une prolifération endothéliale plus ou moins manifeste suivant les glomérules considérés. La lumière capsulaire est souvent encombrée de débris. Exceptionnellement on trouve à ce niveau la présence de substance albuminoïde. Les glomérules contiennent peu d'hématies, assez souvent, ils n'en contiennent pas du tout.

En certains points de la préparation, on note des altérations épithéliales caractérisées par des phénomènes dégénératifs allant jusqu'à la nécrose et par des aspects de régénération apparaissant sous forme de plasmodes.

La lumière des tubes contient presque toujours des cylindres. Quelques uns sont des cylindres hyalins. Ils constituent l'exception. D'autres sont des cylindres granuleux, ils sont constitués soit de débris, soit d'éléments épithéliaux altérés et desquamés, soit d'hématies en voie de lyse. La présence de tels cylindres se trouve avant tout dans la corticale, mais se retrouve également dans les tubes de la médullaire où les cylindres hyalins sont en plus grand nombre que dans la corticale (Planche XI).

Lapin N° 983 (fig. N° 5).

Evolution : Cet animal est le seul du lot témoin qui ait survécu. Il a présenté les mêmes symptômes de choc après l'injection de sérum de canard. Cinq à six jours après l'injection, nous avons constaté une élévation de la pression artérielle

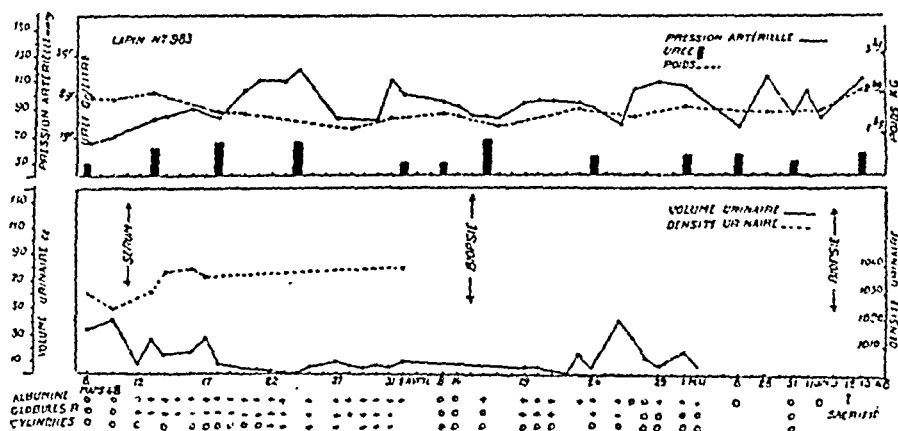


Figure 5.

qui a passé de 75 mm de Hg en moyenne à 100—110 mm de Hg. Au cours des contrôles successifs, pratiqués dans les mois suivants, la pression artérielle s'est maintenue aux environs de 100 mm de Hg. La courbe de poids est restée relativement stationnaire. Nous n'avons pas constaté d'œdème. A la suite de l'injection de sérum, une oligurie est apparue avec albuminurie et hématurie macroscopique. L'albuminurie a persisté pratiquement pendant deux mois et demi, ainsi que l'hématurie, après les trois premiers jours qui ont suivi l'injection de sérum n'a plus été décelable que microscopiquement.

La cylindrurie elle, est apparue 11 jours après l'injection de sérum et a persisté pendant une dizaine de jours. L'animal a subi deux biopsies rénales, l'une un mois après l'injection, la seconde trois mois plus tard. Il a été sacrifié après 7 mois d'observation. L'azotémie, de 0,31 gr pour mille avant l'injection, après avoir passé par un maximum atteignant 0,85 gr pour mille, s'est stabilisée aux alentours de 0,50 gr pour mille.

Autopsie : Rein droit : 11,2 gr.

A part une légère hypertrophie compensatrice, à la suite des biopsies répétées, l'organe présentait un aspect normal macroscopiquement.

Histologie : Première biopsie rénale : Tous les floculus sont plus ou moins intumescents, quelques uns seulement présentent une prolifération endothéliale d'une certaine intensité. Aucun glomérule ne contient dans sa lumière capsulaire de substance albuminoïde ou de débris. Tous les floculus contiennent dans la lumière de leurs anses un nombre normal d'hématies. Il existe des altérations épithéliales discrètes, et la lumière des tubes montre quelques cylindres épithéliaux et hématiques.

Deuxième biopsie rénale : Très importante prolifération endothéliale associée à une intumescence plus ou moins remarquable des floculus. Congestion floculaire variable d'un glomérule à l'autre. Cet ensemble de modifications donne aux glomérules dont le floculus occupe le quasi totalité de l'aire une densité remarquable. Les tubes présentent un aspect normal dans tout l'ensemble de la préparation.

Rein prélevé lors du sacrifice de l'animal : Tous les floculus sont intumescents, mais à des degrés très variables. Quelques uns seulement présentent une hyperplasie endothéliale très marquée. La lumière capsulaire ne contient qu'exceptionnellement quelques débris, mais jamais de substance albuminoïde. Les lumières floculaires contiennent toutes des hématies en quantité normale ou légèrement supérieure à la normale.

Il n'existe pas d'altérations épithéliales évidentes, par contre, un très grand nombre de tubes contiennent en quantité variable des débris dans leur lumière. Il importe de signaler une sclérose de la vitrée des tubes.

B. ANIMAUX TRAITÉS PAR LE PHÉNERGAIS

Lapin N° 994 (fig. N° 6).

Evolution : L'animal, bien que protégé par l'antihistaminique de synthèse, a également présenté quelques symptômes de choc, mais plus atténués que chez les animaux non traités. L'évolution clinique a été en tout point superposable à celle des cinq animaux non traités du même groupe. La mort est survenue après 24 heures. Nous avons constaté également une albuminurie avec hématurie macroscopique, mais pas de cylindrurie. La pression artérielle était imprenable. L'azotémie a passé de 0,42 gr ‰ à 1,48 grs ‰ .

Autopsie : Rein gauche : 9,5 gr.

Rein droit : 9,4 gr.

Les reins étaient œdématisés, gorgés de sang, la structure de parenchyme rénal était méconnaissable. Les autres organes ne présentaient pas de lésions décelables macroscopiquement.

Histologie : Tous les floculus sont fortement intumescents. Quelques uns présentent en outre dans leur lumière capsulaire soit un peu de substance albuminoïde, soit quelques débris. Dans la lumière des anses floculaires on ne

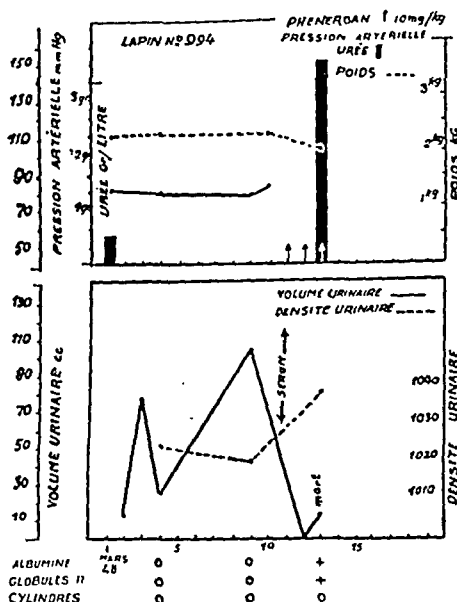


Figure 6.

constate que rarement la présence d'hématies. Certains floculus présentent une tendance nette à la prolifération endothéliale.

On note quelques altérations épithéliales tout à fait segmentaires. Ces altérations sont d'ordre dégénératifs. Dans la lumière des tubes on note la présence soit de cylindre hyalins, soit beaucoup plus souvent, de cylindres granuleux. Dans ce cas il s'agit ou bien de cylindres constitués de débris, ou bien de cylindres constitués d'hématies en voie de lyse. Ces cylindres sont avant tout localisés dans les tubes de la corticale, il en existe quelques uns dans ceux de la médullaire.

Lapin N° 930 (fig. N° 7).

Evolution : Identique à celle de l'animal précédent. La mort est survenue 48 heures après l'injection de sérum. L'azotémie a passé de 0,42 gr % à 3,63 gr %.

Autopsie : Rein gauche : 8,1 gr.

Rein droit : 7,9 gr.

Aspect semblable à celui des reins du lapin N° 984.

Histologie : *Reins* : Les glomérules sont tous fortement intumescents. Assez souvent cette intumescence coïncide avec l'absence de globules rouges dans les

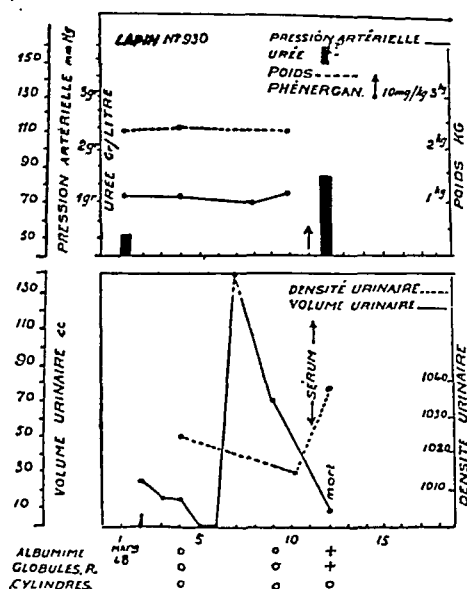


Figure 7.

anses vasculaires. On note dans un certain nombre de glomérules la présence d'une grande quantité de débris, et dans un certain nombre d'autres la présence en grande abondance de substance albuminoïde. Quelques glomérules présentent une morphologie sensiblement normale, ils constituent une rareté.

Les tubes offrent pour la plupart un aspect normal. A titre exceptionnel, quelques uns présentent des altérations épithéliales. Celles-ci sont caractérisées, soit par des aspects dégénératifs, soit par des aspects plasmodiaux. Dans la lumière de presque tous les tubes on note la présence soit de cylindres hyalins, soit de cylindres granuleux constitués de débris. Ces cylindres se retrouvent au niveau des tubes de la médullaire (Planche XII).

Foie : Phénomènes dégénératifs des cellules de la zone péri-portale s'étendant jusqu'à celle de la zone péri-sus-hépatique. Ces phénomènes sont caractérisés par un état granuleux des cytoplasmes dont l'ensemble donne à cette zone un aspect particulièrement clair.

Lapin N° 427 (fig. N° 8).
 Evolution : En tous points comparable aux deux cas précédents. La mort survient en 48 heures. L'azotémie de 0,46 gr %/00 monte à 2,27 gr %/00.

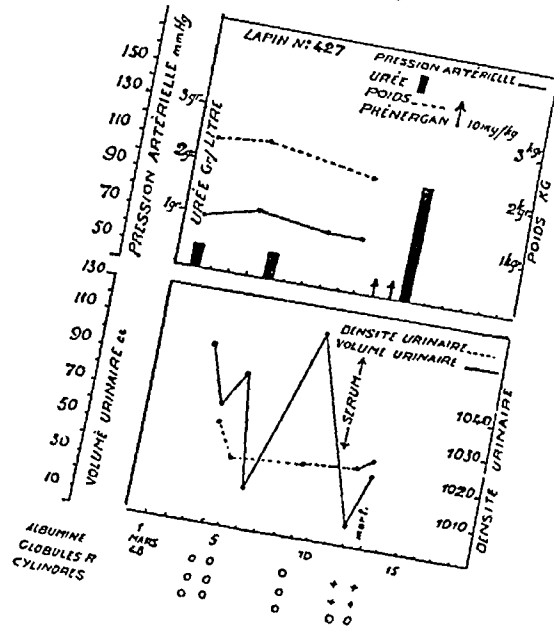


Figure 8.

Autopsie : Rein gauche : 12,1 gr.
 Rein droit : 13,1 gr.

Ils présentent les mêmes caractères que ceux décrits dans les deux cas précédents.

Histologie : Aspect fortement intumescent de tous les floculus, avec prolifération endothéliale plus ou moins importante suivant les glomérules considérés. A ces deux manifestations s'associe soit la présence de substance albuminoïde, soit celle de débris dans la lumière capsulaire.

Quelles que soient les modifications glomérulaires, on note l'absence quasi complète d'hématies dans les anses floculaires.

Les lésions épithéliales sont extrêmement discrètes. Elles sont segmentaires et caractérisées essentiellement par des phénomènes dégénératifs. Par contre, la lumière de presque tous les tubes est occupée par des cylindres dont certains sont des cylindres hyalins et d'autres des cylindres granuleux constitués de débris. Au niveau d'un grand nombre de tubes, on constate la présence de cylindres granuleux constitués d'hématies en voie de lyse. Plus rares sont certains cylindres paraissant constitués par des débris épithéliaux. La présence de

tels cylindres se retrouve tant au niveau des tubes de la corticale qu'à celui de ceux de la médullaire.

Lapin N° 000 (fig. N° 9).

Evolution : Également superposable a celle des animaux

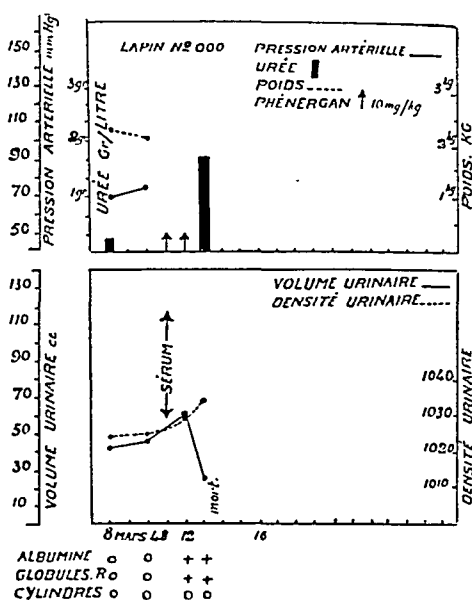


Figure 9.

précédents. La mort survient en 48 heures l'azotémie passe de 0,25 gr ‰ à 1,65 ‰ .

Autopsie : Rein gauche : 11,5 gr.

Rein droit : 10,9 gr.

Nous retrouvons toujours les mêmes aspects que dans les cas précédents.

Histologie : Tous les floculus sont fortement intumescents. Cette intumescence peut être assez intense pour donner un aspect « lavé » au floculus. Elle pourrait ainsi, à première vue, en imposer pour un remaniement fibreux, mais en réalité elle ne prend jamais les colorants du collagène. Elle s'accompagne constamment d'une assez forte prolifération endothéliale. Les anses floculaires ne contiennent pratiquement jamais d'hématies. A côté de ces modifications les plus évidentes, on constate accessoirement la présence de substance albuminoïde ou, beaucoup plus souvent encore, celle de débris dans la lumière capsulaire.

En certains points de la préparation on note quelques altérations épithéliales : celles-ci sont d'ordre dégénératif et sont tout à fait rares. Dans la lumière des tubes on trouve des débris en assez grand nombre. Les cylindres hyalins constituent dans la corticale une exception. Par contre dans la médul-

des glomérules juxta-médullaires qu'au niveau des glomérules sous-capsulaires, où elles font parfois presque défaut. Légère prolifération endothéliale.

On ne trouve pas d'altération des cellules épithéliales et la lumière des tubes ne contient pas de cylindres.

Resumé : Dans ce lot de dix lapins l'action d'un sérum de canard fortement chargé en anticorps antirein déclenche chez les animaux une néphrite de type suraigü avec mort dans huit cas sur dix dans les 48 heures. Du point de vue clinique, la maladie se traduit par une oligurie apparaissant dans les 24 heures qui suivent l'injection de sérum avec albuminurie, hématurie macroscopique, poids spécifique élevé de l'urine. Nous n'avons pas trouvé, il est vrai, de cylindres dans le culot urinaire, alors qu'ils sont présents dans les tubes à l'examen histologique. Nous les avons vu apparaître après dix à douze jours chez les 2 animaux qui ont survécu. L'azotémie, elle, augmente dans des proportions considérables. La pression artérielle était imprenable chez les huit animaux morts dans les 48 heures, alors que nous avons constaté une hypertension nette, survenant après cinq à six jours, chez les deux survivants.

Nous reprendrons dans les conclusions générales la discussion détaillée des similitudes et des différences que présente l'étude des coupes histologique et les déductions que nous pouvons en tirer. Mais nous pouvons déjà constater que l'examen histologique des reins de ces animaux se caractérise principalement : 1° — par l'intumescence des flocculus, d'autant plus intense que les animaux sont morts plus précocément ; 2° — par une prolifération endothéliale plus nettement marquée que dans les autres lots ; 3° — par une anémie foculaire quasi constante ; 4° — par la présence de substance albuminoïde dans la lumière capsulaire des glomérules ; 5° — par la présence de débris d'origine vraisemblablement albuminoïde dans la lumière capsulaire ; 6° — par des lésions épithéliales ; 7° — par la présence de cylindres dans les tubes (Planche XI).

Nous constatons en outre l'inefficacité quasi totale de l'antihistaminique de synthèse sur l'évolution de la maladie et les lésions histologiques (Planche XII).

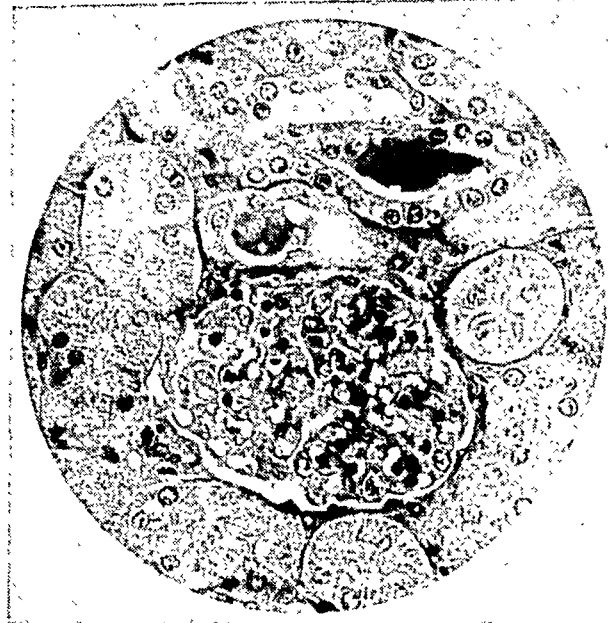


Planche I.

Intumescence glomérulaire. — Épaississement oédémateux des parois capillaires du floculus avec conservation parfaite de l'architecture. Gonflement du bouquet vasculaire qui occupe presque toute l'aire glomérulaire (lapin 930 — Ier lot — mort dans les 24 premières heures de l'expérience — Bleu Masson).

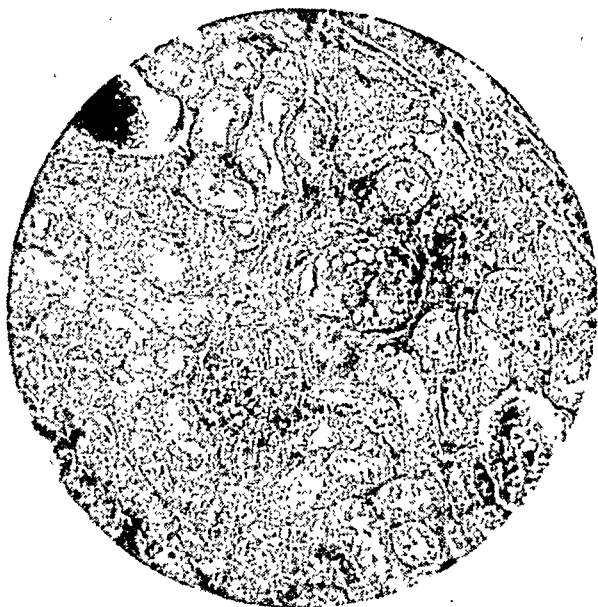


Planche II.

Prolifération endothéliale. — Augmentation très notable du nombre des cellules endothéliales se traduisant par celle de leur noyaux dans l'anse floculaire (lapin 983 — lot I — sacrifié au terme de 210 jours — Bleu Masson).



Planche III.

Sclérose interstitielle du glomérule. — Accentuation de la trame se traduisant par un effacement des éléments de celle-ci et prenant les colorants du collagène. Il ne s'agit ici que d'une lésion extrêmement discrète, nous n'avons jamais constaté des lésions de sclérose interstitielle avancées (lapin 905 — 3ème lot — mort au terme de 180 jours — Bleu Masson).

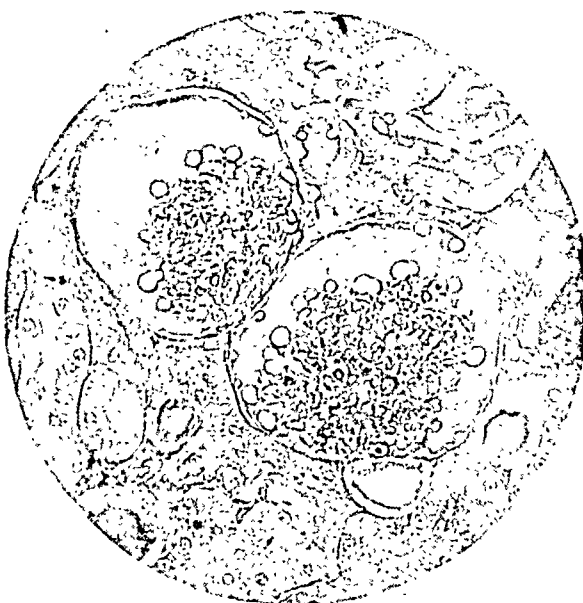


Planche IV.

Présence de substance albuminoïde dans la lumière capsulaire des glomérules. — Noter l'abondance extrême de cette substance, un certain degré prolifération endothéliale et d'anémie des anses glomérulaires ou ne figurent aucun globule rouge. Noter également dans les tubes le présence de cylindres hyalins d'une substance analogue à celle qu'occupe la chambre capsulaire (lapin 930 — Lot I — mort dans les 24 premières heures — Bleu Masson).



Planche V.

Présence de débris dans la lumière capsulaire des glomérules. — Noter leur présence également dans la lumière des tubes où ils constituent une variété de cylindres granuleux (lapin 986 — lot I — mort dans les 48 premières heures — Bleu Masson).



Planche VI.

Lésions dégénératives l'épithélium tubulaire. — Tous les différents aspects de ces lésions se trouvent réunies sur cette figure : dégénérescence granuleuse, vacuolaire, nécrose et desquamation (lapin 986 — lot I — mort dans les 48 premières heures — Bleu Masson).



Planche VII.

Lésions épithéliales. — Foyers de dégénérescence graisseuse (lapin 238 — lot IV — mort au terme de cinq jours — Bleu Masson).

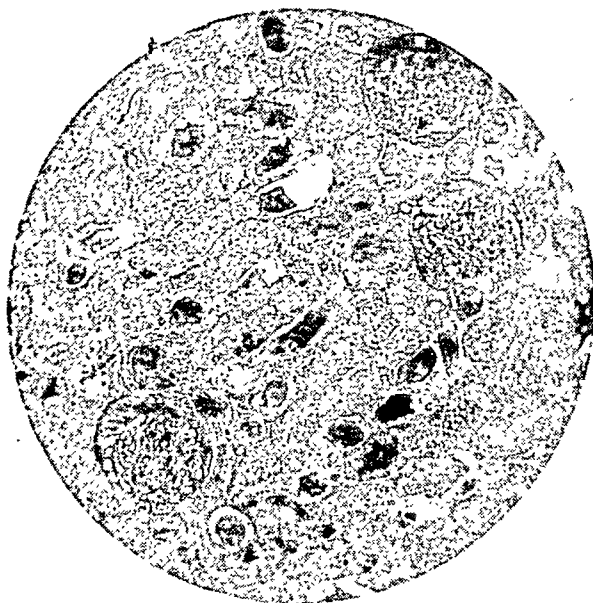


Planche VIII.

Cylindres hyalins. — Présence dans la lumière des tubes de cylindres constitués d'une substance analogue à celle qui occupe la chambre capsulaire de certains glomérules et dont on trouve trois exemples sur ce cliché (lapin 930 — lot I — mort dans les 24 premières heures — Bleu Masson).



Planche IX.

Cylindres granuleux. — Présence dans la lumière des tubes de cylindres constitués de très nombreuses granulations fines analogues à celles que l'on constate assez souvent dans la chambre capsulaire des glomérules. Noter en outre d'importantes et nombreuses altérations épithéliales et quelques aspects de régénération apparaissant sous forme de cellules indifférenciées ou de plasmodes (lapin 427 — lot I — mort dans les 24 premières heures — Bleu Masson).

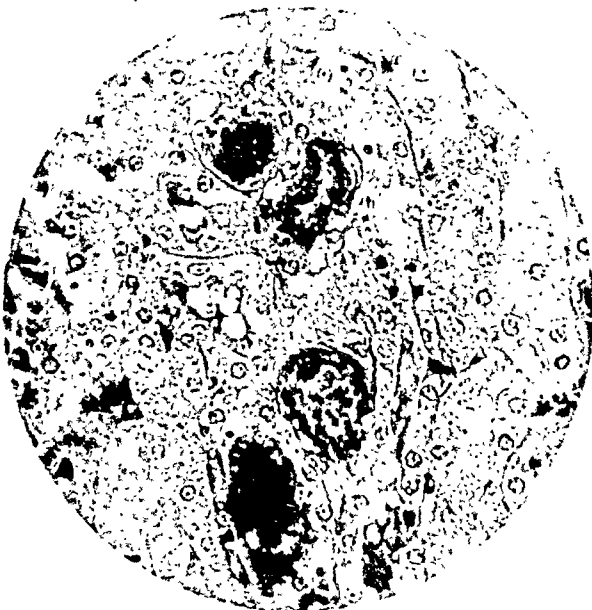


Planche X.

Cylindres granuleux hématiques. — Dans cette variété de cylindres on reconnaît relativement bien des hématis plus ou moins lysées qui permettent d'affirmer leur origine (lapin 994 — lot I — mort dans les 24 premières heures — Bleu Masson).

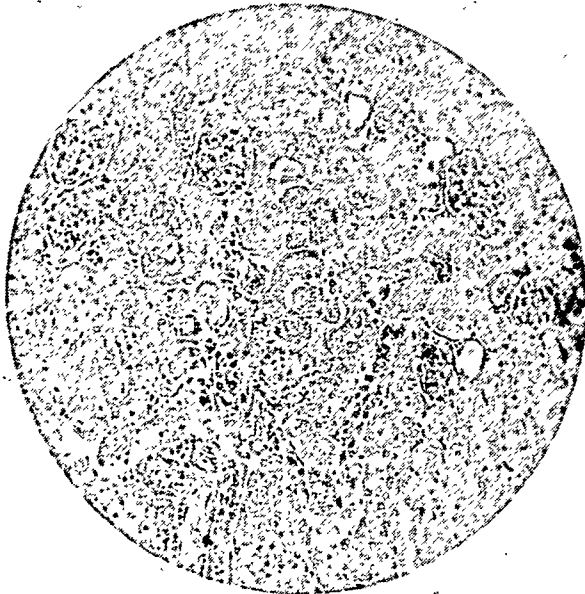


Planche XI.

Vue d'ensemble des lésions obtenues chez un lapin du 1^{er} lot non protégé. — Noter l'intumescence extrême des floculus. La présence de débris dans la chambre capsulaire des glomérules, lésions épithéliales importantes (lapin 500 — mort au terme d'un jour $\frac{1}{2}$ — Bleu Masson).

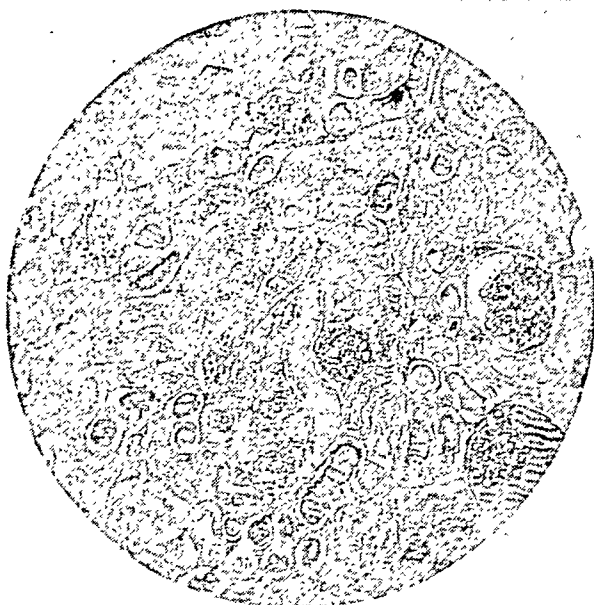


Planche XII.

Vue d'ensemble des lésions chez un lapin du 1^{er} lot traité par le phénérgeais. — Noter l'abondance de substance ou de débris albuminoïde dans les chambres capsulaires des glomérules, les cylindres hyalins, les lésions épithéliales (lapin 930 — mort dans les 24 premières heures — Bleu Masson).

BOOK REVIEW

Pasteur Vallery-Radot: Précis des Maladies Allergiques. 223 p. Editions Médicales Flammarion. 1949.

It seems that there has not previously existed any French handbook of the allergic diseases and problems connected with them. This is all the more remarkable, considering to what extent French scientists have contributed to the creating of modern allergology, its anaphylaxis and development. Just to mention a few: Richet's and his follower's fundamental experimental works on anaphylaxis; Ferdinand Widal's and his followers' clinical research in the field of anaphylaxis and allergy, a research which later has been carried on by Pasteur Vallery-Radot together with several distinguished colleagues and which has resulted in a great number of clinical and experimental works to a great extent of fundamental importance to the development of the allergy research.

The author's thorough knowledge of the anaphylaxis-allergology from the beginning and the development in the last 30-40 years characterize his report and makes it very interesting and instructive reading also from the point of view of the history of the development. The reciprocal relationship between anaphylaxis and allergy and also the existing biological and serological differences are briefly and explicitly described. That is also the case regarding all the many diagnostic and therapeutic subtle and complicated problems which are pertaining to the clinical judgment of the allergic diseases. The book thus gives very instructive though concentrated instructions regarding the preparation and standardization of the allergen extracts; regarding how to perform and measure the skin tests and finally regarding the therapeutic measures which—varying from case to case—are available. The anti-histamine therapeutics are given a special chapter in which their value is judged with justified criticism.

Two great merits of the book ought to be emphasized: the scientific form, giving several data of the experimental anaphylaxis research, as background and foundation of the clinical descriptions, and the desire and ability of giving the allergic diseases the right position as an integrating part of *internal medicine* in its entirety and thereupon ensuing consequences regarding the judgment from etiologic, pathogenic and therapeutic point of view.

Chapter 7 in the book is an important description of the pathological anatomy of the anaphylactic and allergic reactions by P. Gauthier-Villars.

E. B. Salén.



GÖSTA BECKER

In Memoriam.

The allergists in Scandinavia are mourning a great man. Gösta Becker has passed away. A little while ago he was presiding at the Northern Allergy Congress in Helsinki. Here he assembled everybody around him by virtue of his considerate and modest ways, his wise and discreet nature, his kindness and his profound humour. During those fleeting days—filled with scientific endeavour and spent so pleasantly together—none of us could imagine that only two weeks later his life would have drawn to its close.

Gösta Becker was born on 20th April, 1890, in Fredrikshamn. When still a child, he decided on medicine as his profession and he began this task endowed with unusual talents. His rich and lucid intellect, his meticulous punctuality, and his deep understanding of human nature brought him rapidly to the fore both as scientist and as practitioner. Already as

bachelor of medicine he devoted his life to science; his thesis for the degree of M.D. appeared in 1915, a year before he passed his final university examination.

After having practised medicine in Kotka for a few years, he became an assistant at the department of internal medicine at the University Hospital in Helsinki in 1919. Already the following year he was appointed assistant professor of internal medicine at the University of Helsinki, and in 1927 he became professor of the same subject. Gösta Becker was the ideal teacher; his clear and well-written lectures, full of profound humanity, were a firm rock on which many a medical student in Finland could confidently build his further education.

Gösta Becker improved his knowledge by travelling for the purposes of study in different countries, and was asked to lecture by foreign teachers.

The young professor was also employed on social and municipal missions and was entrusted with many commissions because of his wise judgment and authority. He was a member of the Board of Hospitals in Helsinki, the Finnish Academy of Science, the Scientific Central Council of The Finnish Government and he was one of the electors at the presidential elections in 1937 and 1940.

In spite of all these many tasks, he remained true to his scientific interests, and many are the scientific and popularly-written medical works which have come from his pen.

But Gösta Becker was not favoured by Fortune. He was not able to continue his promising career. The bronchial asthma which he had contracted as early as in 1930 was troubling him more and more; in 1938 he left his professor's chair, feeling that his illness did not permit him to attend to his work as regularly and conscientiously as he wished.

Gösta Becker submitted to his fate with equanimity: no one ever heard him complain during the many years that he was struggling day and night with his illness. He always remained its master and soon learned to use his own bitter experiences in allergy for the benefit of his suffering fellow-beings. In 1940 he was persuaded to become doctor

at the Deaconesses' Institution in Helsinki and five years later he was elected head physician—a position he held until his death. Among his suffering patients he grew into the wonderful person who, in the fulfilment of his duty, modestly—sometimes almost imperceptibly—gave of his deep knowledge of life and of his warm understanding to everyone who needed it.

During this time Gösta Becker was appointed member of the boards of many Finnish and foreign scientific societies, such as the Duodecim, the General Society of Physicians in Finland, the "Nordisk förening för Invärtes Medicin" (the Scandinavian Society of Internal Medicine), the "Svenska Läkarsällskapet" (the Swedish Society of Physicians) and the "Nordiska Insulinstiftelsen" (the Nordic Insulin Institution).

His profound understanding of, and insight into the nature of allergic diseases made him one of the most important specialists in allergy in Finland as well as in the whole of Scandinavia. He was one of the founders of the Finnish Society for Allergological Research and was chairman of this society from its beginning. He was also one of the founders of the "Nordisk Förening för Allergiforskning" (the Northern Society for Allergological Research) and a member of its board. At the IIInd Northern Allergy Congress in Helsinki, he was elected chairman of the society. He was also one of the founders of the *Acta Allergologica* and was the Finnish collaborator on this journal. When the "Stiftelsen för Allergiforskning i Finland" (the Finnish Institution for Allergy Research) founded the first Allergy Hospital in Helsinki, in 1946, he was elected chairman of the board of this hospital. He followed the development of this hospital with never-failing interest and entered deeply into all the new plans for improving and centralizing the allergic research. His place will be very hard to fill.

In spite of his great professional interests and his medical practice which he kept to the very last, Gösta Becker found time to devote to art. He was chairman of the Finnish Art

Society from 1943. The many pieces of art, furniture, glass ware and other antiques which he collected in his beautiful home made an impressive setting for his fine, full and many-sided nature.

The world has lost a skilful physician, a rich personality. An irreplaceable friend has left us.

Zaida Eriksson-Lihr.

RECHERCHES SUR LA GENÈSE ET L'ÉVOLUTION DE LA NEPHRITE ALLERGIQUE EXPERIMENTALE ET INFLUENCE DES ANTIHISTAMINIQUES DE SYNTHÈSE SUR CE SYNDROME

(*Suite*)

PAR

B. N. HALPERN, J. TROLLIET et J. MARTIN

II. NEPHRITES AIGUES

(Lapins ayant reçu par voie intra-veineuse 7 cc. de sérum du canard N° 3)

Ce lot comprend huit animaux dont quatre ont reçu l'antihistaminique de synthèse (3.277 R. P.) aux mêmes doses et rythme que les animaux du premier lot.

A. ANIMAUX TÉMOINS

Lapin N° 105 (fig. N° 11).

Evolution : A la suite de l'injection de sérum, l'animal n'a pas présenté de symptômes de choc. L'animal est mort 28 heures après l'injection, durant la nuit, ce qui ne nous a pas permis de prélever du sang pour un second dosage d'urée. Là encore, nous avons constaté une oligurie avec albuminurie et hématurie macroscopique sans cylindrurie, une augmentation nette du poids spécifique urinaire. La pression artérielle était intenable.

Autopsie : Rein gauche : 6,7 gr.

Rein droit : 6,8 gr.

Reins œdématisés, gorgés de sang, rouges sombres. Les autres organes ne présentaient pas d'altération macroscopiquement décelable.

Histologie : Rein : Tous les floculus sont fortement intumescents. Cette intumescence s'accompagne presque toujours d'une prolifération endothéliale plus ou

moins importante suivant les glomérules considérés. Le nombre des hématies dans les anses floculaires est au moins égales et quelquefois même supérieur à la normale. On note quelquefois dans la lumière capsulaire la présence de débris. Il n'y a pas de lésions épithéliales et la lumière des tubes ne contient pas de cylindres.

Foie : Forte dilatation des veines sus-hépatique avec distention des sinus inter-trabéculaires des zones péri-sus-hépatiques.

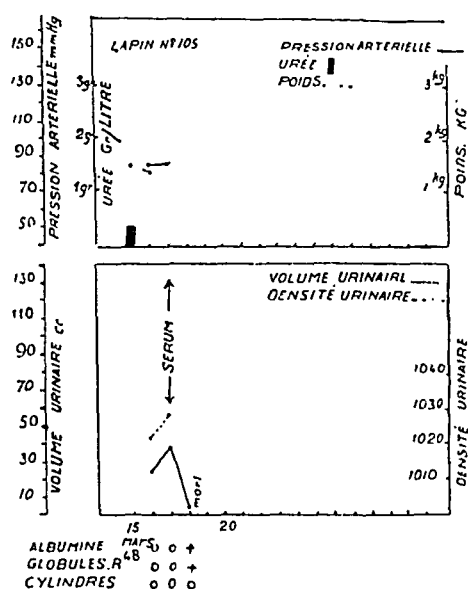


Figure 11.

Lapin N° 108 (fig. N° 12).

Evolution : En tous points superposable au cas précédent. La mort est également survenue au bout de 24 heures, et, pour les mêmes raisons que pour le lapin N° 105, nous n'avons pas pu procéder à un second dosage d'urée.

Autopsie : Rein gauche : 8 gr.

Rein droit : 7,8 gr.

Ils présentent les mêmes caractéristiques que ceux du cas précédent.

Histologie : *Rein* : Franche intumescence de tous les floculus présentant des variations d'intensité segmentaires. Hyperplasie endothéliale également variable suivant les segments considérés. Présence d'hématies en nombre normal au niveau des glomérules sous-capsulaires, et en nombre très inférieur à la normale ou même absence complète d'hématies au niveau des glomérules juxta-médul-

lares. Présence de débris peu nombreux dans la lumière capsulaire de quelques glomérules.

Quelques tubes présentent des altérations épithéliales nécrotiques. Ils sont tout à fait rares. Dans la lumière de quelques uns d'entre eux, on note la présence de cylindres constitués de débris. Certains de ceux-ci sont formés d'hématies en voie de lyse. Ils sont un peu plus nombreux que les cylindres

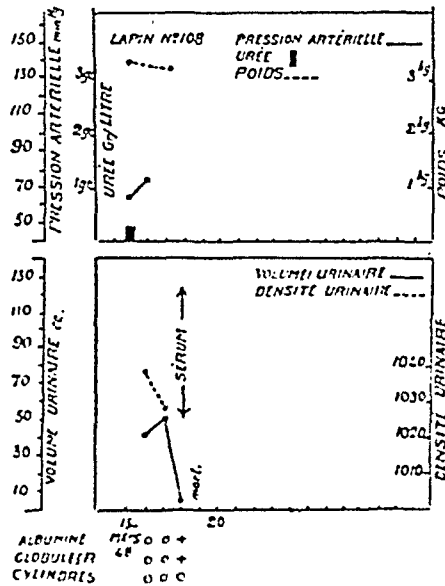


Figure 12.

constitués de débris. Ces cylindres se retrouvent aussi bien au niveau de la médullaire qu'au niveau de la corticale.

Foie : Légère étalement fibreux des espaces portes avec expansion bi-portale tendant à créer une lobulation artificielle.

Lapin N° 107 (fig. N° 13).

Evolution : Similaire aux cas précédents. La mort est survenu en 24 heures. L'azotémie a passé de 0,20 gr %₁₀₀ à 1,75 gr %₁₀₀.

Autopsie : Rein gauche : 8,1 gr.

Rein droit : 8,2 gr.

Les reins présentaient le même aspect que dans les cas précédents.

Histologie : Rein : Très forte intumescence de tous les floculus avec importants phénomènes de prolifération endothéliale. Présence d'hématies en nombre souvent un peu supérieur à la normale au niveau des glomérules sous-capsu-

lares, diminution du nombre ou le plus souvent absence complète d'hématies au niveau des glomérules juxta-médullaires. Ni substance albuminoïde, ni débris dans les lumières capsulaires.

Quelques tubes seulement présentent des phénomènes de nécrose épithéliale discrète. Le plus grand nombre des tubes contiennent dans leur lumière des cylindres. Les uns sont constitués de débris, les autres d'hématies lysées. Très

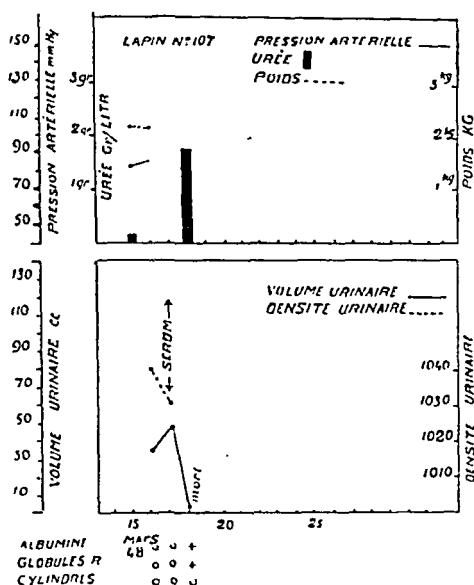


Figure 13.

exceptionnellement quelques cylindres sont hyalins. La présence de ces cylindres se retrouve jusqu'au dernier segment du tube, c'est à dire au sommet de la pyramide (Planche XIII).

Foie : normal.

Lapin N° 106 (fig. N° 14).

Evolution : Cet animal a survécu à l'injection de sérum. Il a présenté, de façon plus atténuée, les mêmes symptômes que les lapins N° 983 et 987 du premier lot : hypertension, azotémie, oligurie pendant les 8 jours qui ont suivi l'injection de sérum avec albuminurie, hématurie et cylindrurie. Il a subi deux biopsies rénales, l'une 29 jours après l'injection de sérum, la seconde 55 jours plus tard. Il est mort 2 jours après la seconde intervention.

Autopsie : Rein droit : 10,3 gr.

Aspect macroscopique normal, à l'exception d'une certaine hypertrophie compensatrice à la suite des biopsies du rein gauche.

Histologie : *Première biopsie rénale* : très forte intumescence de tous les floculus avec ou sans phénomènes notables d'hyperplasie endothéliale. Absence complète de substance albuminoïde ou de débris dans la lumière capsulaire. Un très grand nombre de glomérules ne contiennent aucune hématie. Cette absence

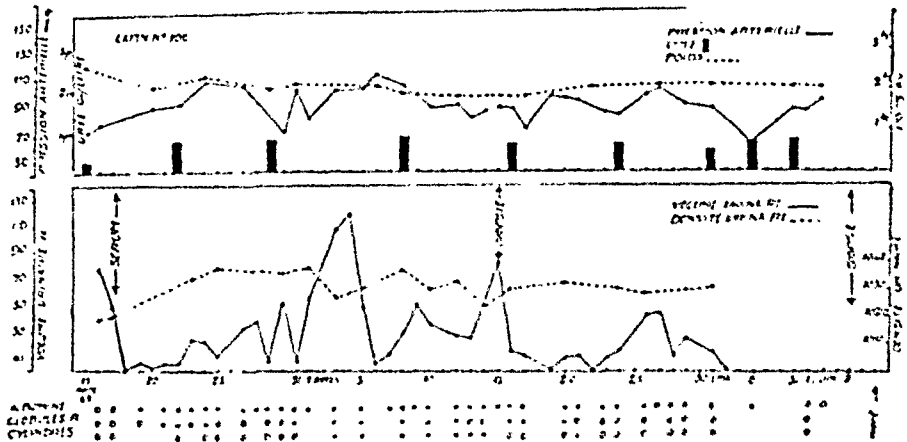


Figure 14.

d'hématies dans les anses floculaires semble marcher de pair avec l'intensité de l'intumescence des parois capillaires.

On ne met en évidence ni lésion épithéliale, ni cylindres dans la lumière des tubes.

Deuxième biopsie rénale : forte hyperplasie endothéliale suivant les glomérules considérés. Très léger remaniement de sclérose interstitielle de quelques glomérules. Assez forte congestion de ceux des floculus dont la trame n'est pas modifiée. Ni substance albuminoïde, ni débris dans les lumières capsulaires.

Pas de lésions épithéliales. Pas de cylindres hyalins ou granuleux dans la lumière des tubes.

B. ANIMAUX TRAITÉS PAR LE PHÉNERGAN

Lapin N° 104 (fig. N° 15).

Évolution : L'injection de sérum a déclenché, elle aussi, une oligurie avec albuminurie et hématurie ainsi qu'une élévation notable du poids spécifique urinaire. Durant les 12 jours où l'animal a survécu, nous n'avons pas constaté de cylindres

Histologiquement les lésions sont caractérisées essentiellement 1° — par une intumescence des flocculus. 2° — par une prolifération endothéliale moins accusée dans l'ensemble que dans le premier lot. 3° — par la présence de débris d'origine vraisemblablement albuminoïde dans les lumières capsulaires pour autant que les animaux soient morts précocement. 4° — par des lésions épithéliales visibles également chez les animaux morts dans les 24 heures suivant l'injection. 5° — par la présence de cylindres dans les tubes.

Sans pouvoir tirer de conclusions définitives, nous devons constater que 3 sur les 4 animaux non protégés sont morts dans les 24 heures qui ont suivi l'injection de sérum, alors qu'un lapin sur 4 seulement parmi les animaux protégés, est mort dans les 12 jours qui ont suivi l'injection. L'antihistaminique de synthèse aurait-il une action protectrice, bien qu'il n'agisse pas d'une façon apparente sur l'évolution clinique de la maladie ni, pour autant que l'on puisse en juger, sur les lésions histologiques ? Il est probable, que cette action protectrice porte surtout sur les symptômes anaphylactoïdes.

III. NEPHRITES SUBAIGUES

(Lapins ayant reçu par voie intraveineuse deux injections, de 5 cc. chacune, de sérum des canards N° 2 & 4, à 15 jours d'intervalle)

Ce lot comprend 10 animaux dont 5 ont été protégés par l'antihistaminique de synthèse (3.277 R. P.), toujours à raison d'une injection sous-cutanée de 10 mg/kg et par jour. Les animaux n'ont pas présenté de symptômes de choc à la suite de l'injection de sérum. Nous avons décidé, devant la pauvreté du tableau clinique de faire une seconde injection de sérum de canard ayant le même taux d'anticorps antirein que celui employé lors de la première injection, dans le but de voir si cette seconde injection déclencherait l'apparition de symptômes plus nets.

A. ANIMAUX TÉMOINS

Lapin N° 906 (fig. N° 19).

Evolution : A la suite de l'injection de sérum, l'animal a présenté une oligurie avec albuminurie, hématurie macroscopique et cylindrurie 10 jours après l'injection. La pression ar-

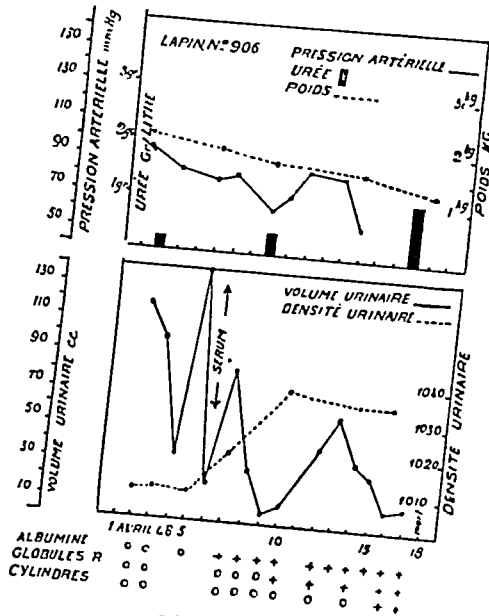


Figure 19.

térielle n'a pratiquement pas variée durant les 13 jours où l'animal a survécu. L'azotémie a passé elle de 0,24 gr %₀₀ à 1,11 gr %₀₀.

Autopsie : Rein gauche : 5,7 gr.

Rein droit : 6 gr.

L'aspect en est macroscopiquement normal. Les autres organes ne présentent pas de lésions macroscopiquement constatables.

Histologie : Rein : Forte intumescence de tous les floculus associée ou non à des phénomènes de prolifération endothéliale d'intensité variable. Certains floculus sont gorgés d'hématies. D'autres au contraire en sont pratiquement privés. Ces derniers siègent le plus souvent dans la zone juxta-médullaire. Présence de débris dans la lumière capsulaire de la quasi totalité des glomérules. Lésions extrêmement partielles et segmentaires de l'épithélium des tubes caractérisées

par des phénomènes de nécrose avec desquamation. Présence dans la lumière des tubes de nombreux cylindres granuleux constitués de débris.

Foie : Sensiblement normal, très léger étalement fibreux des espaces portes.

Lapin N° 225 (fig. N° 20).

Evolution : Nous avons constaté en plus des symptômes

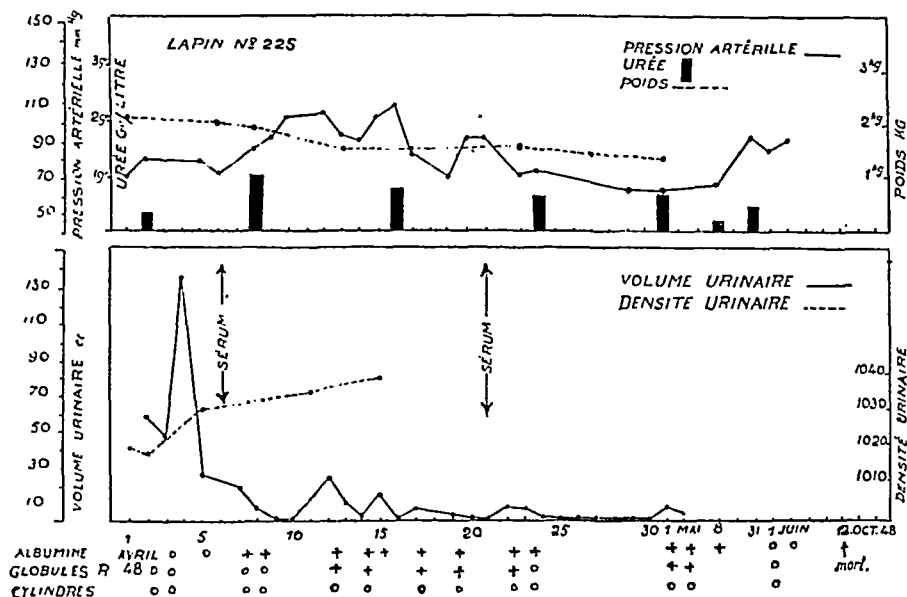


Figure 20.

urinaires une élévation de la pression artérielle qui a passé de 73 mm Hg en moyenne à 105 mm Hg, 3 jours après la première injection de sérum. Elle est revenue progressivement à la normale dans les semaines qui ont suivi. L'azotémie a passé de 0,32 gr % à 0,71 gr % au cours de l'évolution pour redescendre à 0,45 gr % deux mois plus tard. Nous n'avons jamais constaté de cylindrurie, même après la seconde injection de sérum de canard. L'animal est mort après 6 mois.

Autopsie : Rein gauche : 7,1 gr.

Rein droit : 6,8 gr.

L'aspect macroscopique des reins est normal.

Histologie : Très forte intumescence de la presque totalité des floculus avec phénomènes de prolifération endothéliale. Les floculus contiennent un nombre

normal d'hématies dans leur ensemble. Léger remaniement interstitiel fibreux de quelques glomérules, sans modification notable de la capsule. Au niveau de presque toutes les lumières capsulaires on note la présence de débris. Pas de lésions épithéliales. Rares cylindres granuleux constitués de débris dans la lumière des tubes qui correspondent aux glomérules qui en présentent eux mêmes dans la lumière de leur capsule.

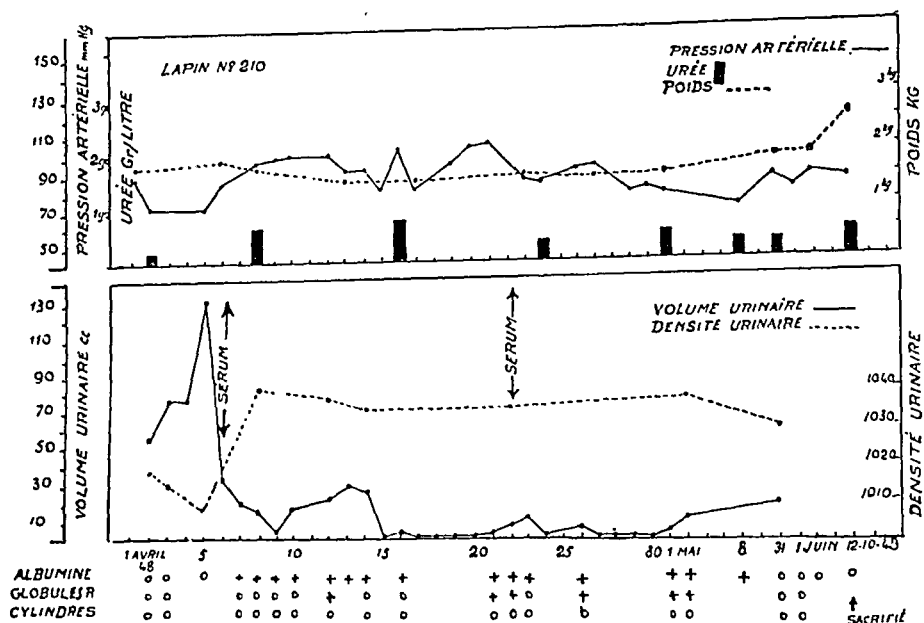


Figure 21.

Lapin N° 210 (fig. N° 21).

Evolution : Semblables à tous points à celle du cas précédent. L'animal a été sacrifié après 6 mois.

Autopsie : Rein gauche : 7,2 gr.

Rein droit : 7 gr.

Aspect macroscopique normal.

Histologie : Rein : Intumescence de tous les floculus avec phénomènes très notables de prolifération endothéliale. Remaniement fibreux interstitiel assez manifeste de la presque totalité des floculus avec, ou plus souvent, sans épaississement scléreux de la capsule de Bowmann. Présence d'hématies en nombre sensiblement inférieur à la normale dans la lumière des anses d'un assez grand nombre de floculus. Au niveau de quelques uns d'entre eux, au contraire, leur présence y est en nombre supérieur à la normale. Ni débris, ni substance albuminoïde dans les lumières capsulaires.

On ne note pas d'altérations épithéliales. Les tubes ne contiennent pas de cylindre.

Foie : Foie normal.

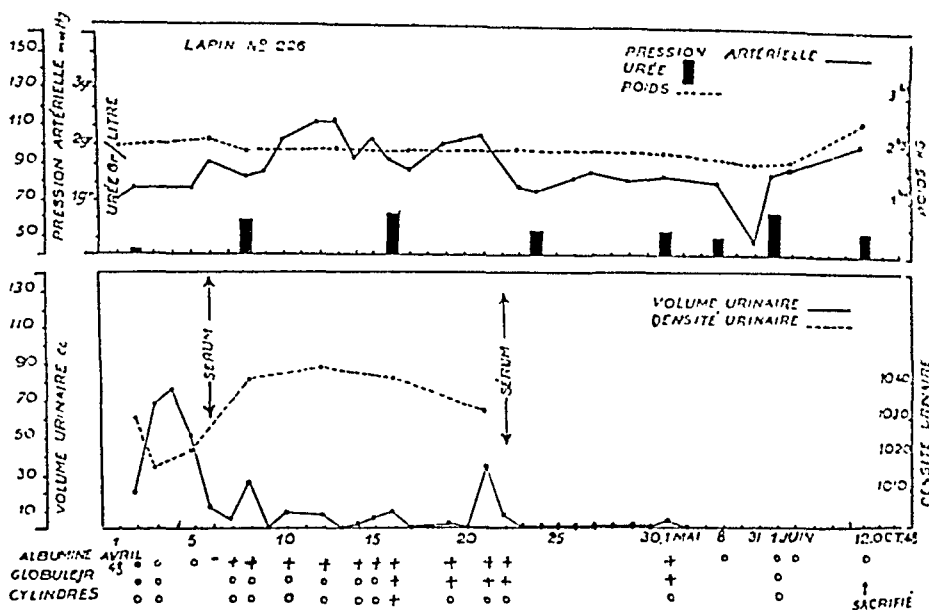


Figure 22.

Lapin N° 226 (fig. N° 22).

Evolution : Comparable aux deux cas précédents. L'animal a été sacrifié après six mois.

Autopsie : Rein gauche : 7,3 gr.

Rein droit : 7,6 gr.

Aspect macroscopique normal.

Histologie : Très forte intumescence de la quasi totalité des floculus avec phénomènes importants de prolifération endothéliale, tout au moins au niveau du plus grand nombre d'entre eux. La plupart des floculus contiennent un nombre normal ou légèrement supérieur à la normale d'hématies. Quelques uns seulement, dans la zone juxta-médullaire, en sont pauvres ou privés. Léger remaniement interstitiel fibreux de quelques glomérules sans modification de la capsule. Présence de débris en nombre variable au niveau de presque toutes le lumières capsulaires.

Pas de lésions épithéliales. Présence de cylindres granuleux constitués de débris dans la lumière des tubes correspondant aux quelques glomérules qui en présentent eux mêmes dans la lumière de leurs capsules.

Rein prélevé à la mort de l'animal : intumescence relative des anses au niveau d'un certain nombre de floculus tendant à présenter une topographie lobulaire au sein des floculus. A cette intumescence segmentaire s'associe inconstamment des phénomènes de prolifération endothéliale d'une part et des phénomènes de remaniement interstitiel fibreux discret de la trame d'autre part. Cette dernière altération s'accompagne quelquefois de façon plus ou moins évidente d'un épaissement fibreux discret de la capsule de *Bowmann*. Ni substance albuminoïde, ni débris dans les lumières capsulaires. Très peu d'hématies dans la lumière des anses floculaires.

On ne note pas d'altérations épithéliales. La lumière des tubes ne contient pas de cylindres.

Foie : Elargissement fibreux discret des espaces portes avec quelques expansions fibreuses dans le parenchyme. Forte dilation veineuse. Important œdème des parois artérielles sans phénomène de lyse.

B. ANIMAUX TRAITÉS PAR LE PHÉNERGAN

Lapin N° 901 (fig. N° 24).

Evolution : L'animal a fait, à la suite de l'injection de sérum, une oligurie avec albuminurie. L'hématurie et la cylindrurie, intermittentes, sont apparues deux à trois jours après l'injection de sérum. La pression artérielle de 70 mm Hg en moyenne a passé à 120 mm Hg 5 jours après l'injection. L'azotémie a passé de 0,30 gr ‰ à 0,85 gr ‰ la veille de la mort de l'animal, soit après 12 jours. L'animal a subi une biopsie rénale le 10^{ème} jour après injection.

Autopsie : Rein gauche : 6,7 gr.

Rein droit : 6,5 gr.

Aspect macroscopique normal.

Histologie : Biopsie rénale : un assez grand nombre de floculus sont légèrement intumescents. Les autres sont franchement normaux. Légère prolifération endothéliale marchant de pair avec le degré d'intumescence. On ne note ni substance albuminoïde ni débris dans les lumières capsulaires. Les glomérules dans leur ensemble contiennent peu d'hématies. Un certain nombre d'entre eux n'en contiennent pas du tout.

On ne constate aucune lésion épithéliale et la lumière des tubes ne contient pas de cylindres.

Rein prélevé à la mort de l'animal : aspect intumescents de tous les floculus, d'intensité variable suivant ceux que l'on considère. Légère prolifération endothéliale. Tous les floculus contiennent des hématies, certains en nombre nette-

ment supérieur à la normale. Quelques glomérules contiennent dans leur lumière capsulaire un certain nombre de débris, mais jamais de substance albuminoïde.

On ne note pas d'altérations épithéliales. Il n'y a pas de cylindre dans la lumière des tubes, qu'il s'agisse de ceux de la corticale ou de ceux de la médullaire.

Foie : Très léger étalement scléreux des espaces portes avec quelquefois ébauches d'expansions fibreuses bi-veineuses.

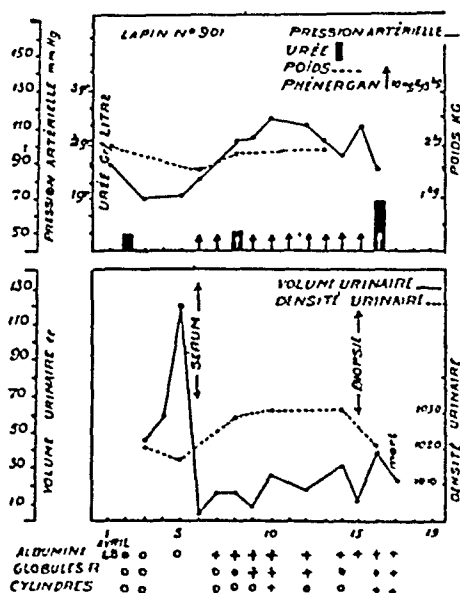


Figure 24.

Lapin N° 903 (fig. N° 25).

Evolution : Pratiquement superposable à celle de l'animal précédent, à l'exception de la pression artérielle qui n'a pas augmenté et de l'absence de cylindrurie. La mort est survenue 5 jours après l'injection du sérum. L'azotémie a passé de 0,27 gr $^{\circ}/_{00}$ à 1,54 gr $^{\circ}/_{00}$.

Autopsie : Rein gauche : 6,3 gr.

Rein droit : 6,7 gr.

Aspect macroscopique normal.

Histologie : Intumescence légère de tous les flocculus avec ou sans prolifération endothéliale. Les anses capillaires contiennent toujours des hématies, mais tandis qu'au niveau de certains flocculus elles en contiennent peu, au niveau de certains autres, elles en contiennent un nombre supérieur à la normale.

Absence complète de débris ou de substance albuminoïde dans la lumière capsulaire.

Il existe des lésions épithéliales discrètes caractérisées soit par des phénomènes de nécrose cellulaires suivie de desquamation, soit, en certaines régions, par un état vacuolaire des protoplasmes, intéressant particulièrement les tubes contournés et témoignant d'un état de dégénérescence graisseuse. Dans la corti-

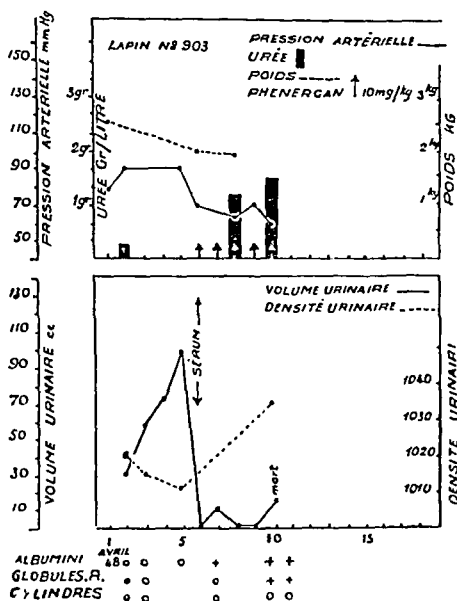


Figure 25.

cale on ne note pas de cylindre dans la lumière des tubes. Dans la médullaire par contre, on note la présence d'assez nombreux cylindres hyalins (Planche XVI).

Lapin N° 905 (fig. N° 26).

Evolution : Cet animal a survécu pendant 4 mois et 3 semaines. Durant le premier mois, l'animal a présenté une oligurie prononcée, rendant les contrôles urinaires chimiques et microscopiques difficiles. L'albuminurie cependant a été constante chaque fois où elle a pu être contrôlée. L'hématurie et la cylindrurie ont été plus inconstantes. La pression artérielle, après une poussée hypertensive dans les jours qui ont suivi l'injection, s'est stabilisée aux alentours de 90 mm Hg. L'azotémie a passé de 0,23 gr $\%$ à 0,68 gr $\%$ après 2 mois pour retomber à 0,31 gr $\%$ après 3 mois.

Autopsie : Rein gauche 6,5 gr.

Rein droit : 6,8 gr.

Aspect macroscopique normal.

Histologie : Très forte intumescence de tous les flocculus avec aspect « lavé » de beaucoup d'entre eux. Prolifération endothéliale discrète. Présence en nombre variable ou absence fréquente d'hématies dans la lumière des anses capillaires.

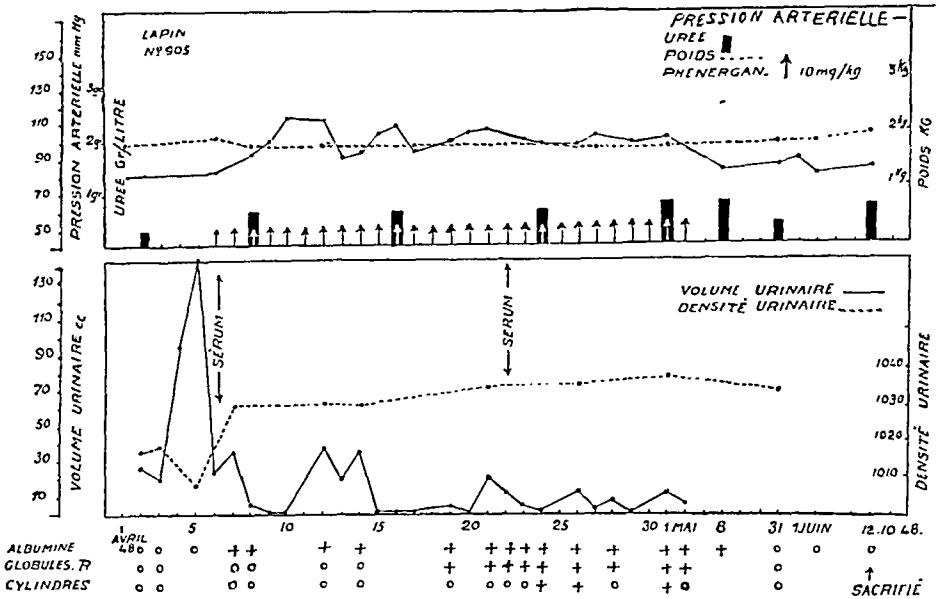


Figure 26.

Présence au niveau de quelques glomérules de débris dans la lumière capsulaire.

On ne note pas d'altérations épithéliales ni de cylindres dans la lumière des tubes.

Lapin N° 902 (fig. N° 27).

Evolution : A part une oligurie moins marquée, l'évolution est très semblable au cas précédent. La seconde injection de sérum a provoqué une accentuation des signes urinaires (albuminurie, hématurie, cylindrurie). La pression artérielle est restée fixée aux alentours de 100 mm Hg. L'azotémie qui était de 0,31 gr % au départ s'est fixée à 0,60 gr % en moyenne. L'animal a été sacrifié après 6 mois et une semaine.

Autopsie : Rein gauche : 6,5 gr.

Rein droit : 6,6 gr.

Aspect macroscopiques normal.

Histologie : Rein : Très forte intumescence de tous les floculus avec importants phénomènes de prolifération endothéliale. Présence en nombre normal ou supérieur à la normale d'hématies dans la lumière des anses floculaires. Absence

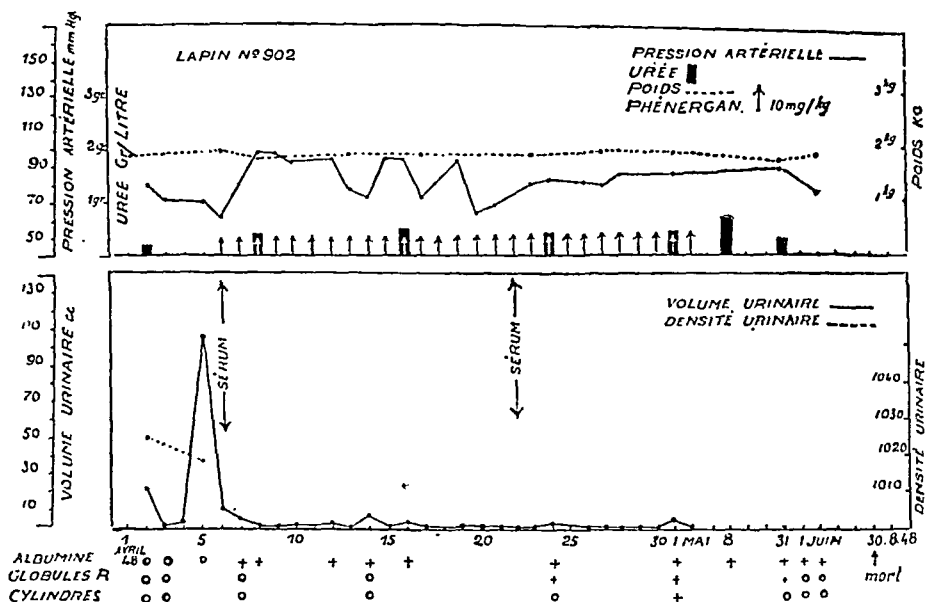


Figure 27.

complète de débris ou de substance albuminoïde dans les lumières capsulaires. A titre de très grande exception on note au niveau de quelques glomérules une légère sclérose interstitielle avec épaississement fibreux discret de la capsule de Bowman.

Il n'existe ni lésions épithéliales, ni cylindres dans la lumière des tubes.

Foie : Le foie est sensiblement normal.

Lapin N° 908 (fig. N° 28).

Evolution : Superposable à celle des animaux précédents avec cependant des signes urinaires plus accusés dès le début. On note également une hypertension nette à 120—130 mm Hg, et l'azotémie a passé de 0,30 gr % à 1,45 gr % le jour de la mort, soit 3 semaines après l'injection de sérum.

Autopsie : Rein gauche : 5,2 gr.

Rein droit : 5,8 gr.

Aspect macroscopiquement normal.

Histologie : Assez forte intumescence de tous les floculus, associée le plus

Histologie : Rein : Assez forte intumescence de tous les floculus, associée le plus souvent à une prolifération endothéliale très notable. Quelques uns d'entre

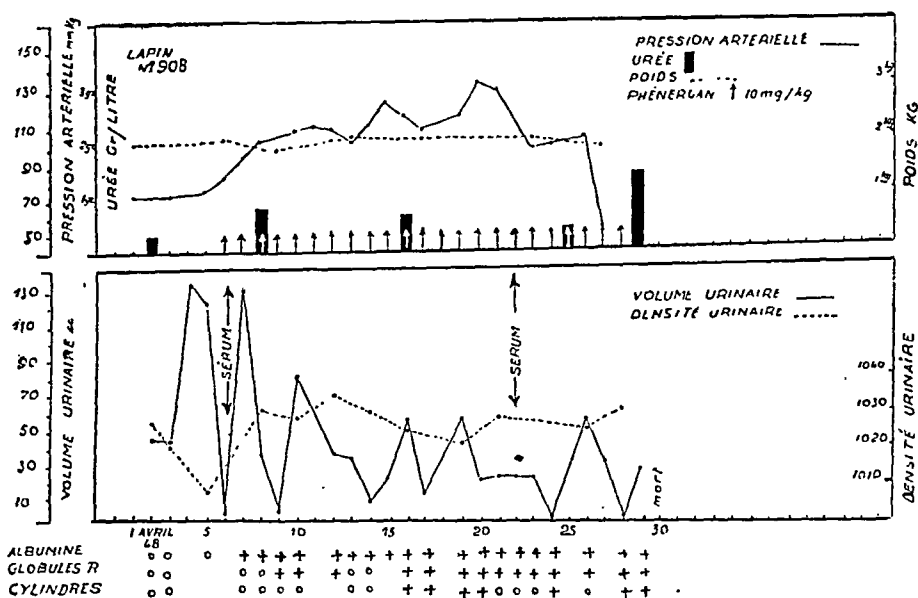


Figure 28.

eux subissent un remaniement fibreux interstitiel discret. Tous les floculus contiennent des hématies, quelques uns en contiennent peu, d'autres au contraire en contiennent un nombre très franchement supérieur à la normale. Beaucoup de glomérules contiennent dans leur lumière capsulaire d'assez nombreux débris.

On ne constate aucune lésion épithéliale. Certains tubes contiennent dans leur lumière des cylindres faits de débris. Ceux-ci sont quelquefois même assez nombreux.

Foie : Foie normal dans son ensemble.

Résumé : Les animaux de ce lot, injectés à deux reprises avec des sérums de canards faiblement chargés en anticorps ont fait une néphrite très atténuée, que même la seconde injection de sérum n'a pas influencée. Les signes urinaires sont relativement discrets et de façon générale, chez les animaux qui ont survécu, on constate après une poussée hypertensive,

une tendance nette de la pression artérielle à se stabilier à la limite supérieure de la normale. L'azotémie, elle, reste en revanche augmentée.

Histologiquement, les lésions sont toujours caractérisées 1° — par l'intumescence des floculus. 2° — par la prolifération endothéliale. 3° — par une anémie foculaire beaucoup moins marquée que dans les 2 lots précédents. 4° — la présence de débris d'origine vraisemblablement albuminoïde dans les lumières capsulaires. 5° — par une sclérose interstitielle du glomérule beaucoup plus nette dans ce groupe d'animaux que dans les précédents où elle est exceptionnelle. 6° — par des lésions épithéliales discrètes.

L'effet de l'antihistaminique de synthèse sur l'évolution de la maladie et des lésions paraît ici absolument nul.

IV. LOT TEMOIN

(Lapins ayant reçu une injection par voie intraveineuse de 6 cc de sérum de canard normal)

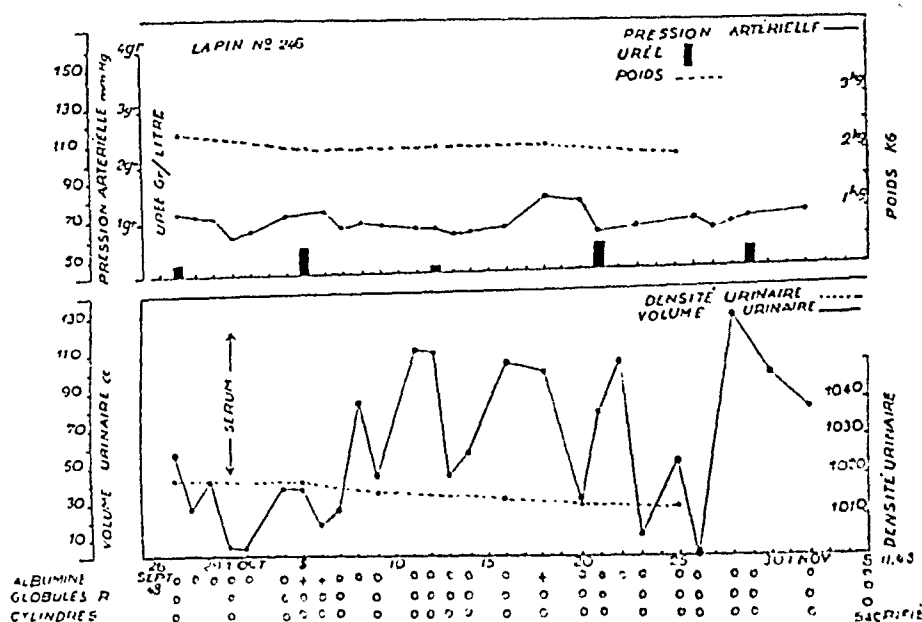
Ce lot comprend 10 animaux chez lesquels nous avons suivi durant 40 jours l'effet d'une injection de sérum de canard normal, ne contenant donc pas d'anticorps antirein.

Aucun des animaux témoins n'a été traité par l'antihistaminique de synthèse. Sur les 10 lapins, deux sont morts de pneumonie, l'un 6 jours après l'injection de sérum, l'autre 25 jours après l'injection. Les animaux ont parfaitement bien supporté l'injection de sérum, et n'ont présenté aucun symptôme de choc. La courbe de poids est restée stationnaire. L'injection a été suivie pendant 2 à 3 jours d'une oligurie durant laquelle les lapins ont présenté, dans la majorité des cas, une albuminurie transitoire, sans hématurie ni cylindrurie. L'azotémie est restée pratiquement constante lors des différents contrôles. La pression artérielle n'a pas variée. La moitié du lot des animaux a subi une biopsie de contrôle 12 jours après l'injection de sérum.

Les graphiques de l'évolution de la maladie étant parfaitement superposables les uns aux autres, nous nous sommes contentés d'en reproduire seulement 6 sur les 10.

Lapin N° 246 (fig. N° 29).

Evolution : Elle est schématisée par la fig. N° 29.



Lapin N° 247 (fig. N° 30).

Evolution : En tous points superposables à celle de l'animal précédent.

Autopsie : Rein gauche : 6,5 gr.

Rein droit : 6,6 gr.

Aspect normal.

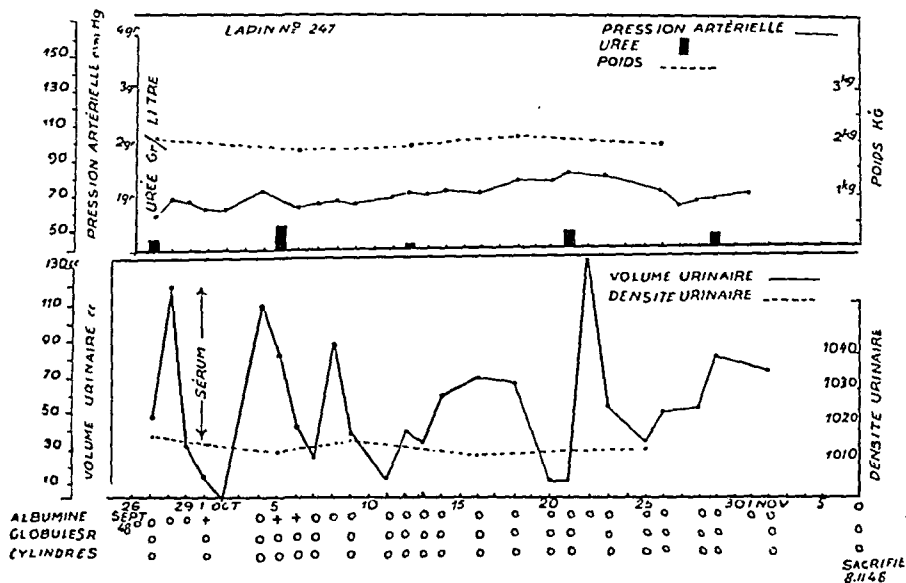


Figure 30.

Histologie : Rein : Intumescence relative de quelques flocculus avec phénomènes de prolifération endothéliale plus ou moins marqués suivant les glomérules considérés. La plupart des glomérules ne contiennent pas d'hématies ou en contiennent un nombre très inférieur à la normale. A titre tout à fait exceptionnel, on peut constater la présence de débris peu nombreux dans la lumière capsulaire de quelques rares glomérules.

Il n'y a pas de lésions épithéliales.

Foie : État granuleux des protoplasmes sans altérations nucléaires, prédominant manifestement dans la zone péri-sus-hépatique dont la veine centrale est très notablement dilatée.

Lapin N° 017 (fig. N° 31).

Evolution : Identique aux cas précédents.

Autopsie : Rein gauche : 7 gr.

Rein droit : 6,8 gr.

Aspect normal.

Histologie : Rein : Forte intumescence des floculus avec phénomènes de prolifération endothéliale variables suivant les glomérules considérés. Absence ou présence en nombre très inférieur à la normale d'hématies dans la lumière des anses capillaires du floculus.

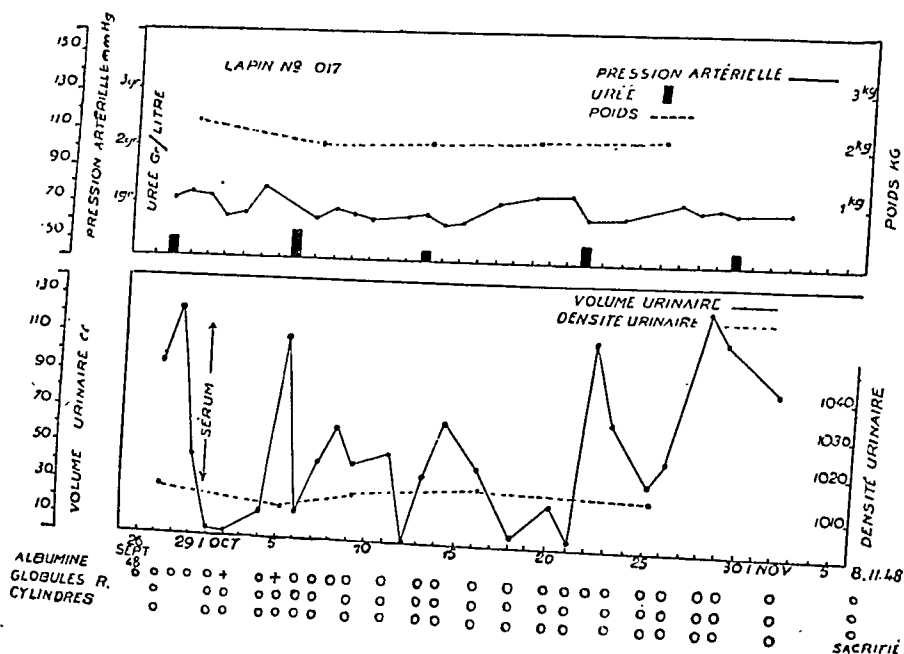


Figure 31.

Il n'existe pas de lésions épithéliales. Présence tout à fait exceptionnelle de cylindres granuleux constitués de débris dans la lumière de certains tubes.

Foie : Très forte dilatation des veines, qu'il s'agisse des veines portes ou des veines sus-hépatiques. Etat granuleux de toutes les cellules, sans altérations nucléaires.

Lapin N° 240 (fig. N° 32).

Evolution : Similaire aux cas précédents. Le lapin a subi une biopsie le 12^{ème} jour après l'injection de sérum.

Autopsie : Rein droit : 8,2 gr.

Aspects macroscopique normal. Les autres organes ne présentent pas de lésions décelables macroscopiquement.

Histologie : *Biopsie rénale* : intumescence relative de presque tous les floculus. Présence en nombre normal ou légèrement inférieur à la normale

Histologie : Biopsie rénale : Très légère intumescence des floculus associée à une prolifération endothéliale très variable en intensité d'un glomérule à l'autre. La lumière des anses capillaires ne contient généralement pas d'hématies. Les lumières capsulaires ne contiennent ni débris ni substance albuminoïde.

Pas de cylindres dans la lumière des tubes, mais quelques tubes présentent à titre exceptionnel des cellules offrant un aspect dégénératif (Planche XVII).

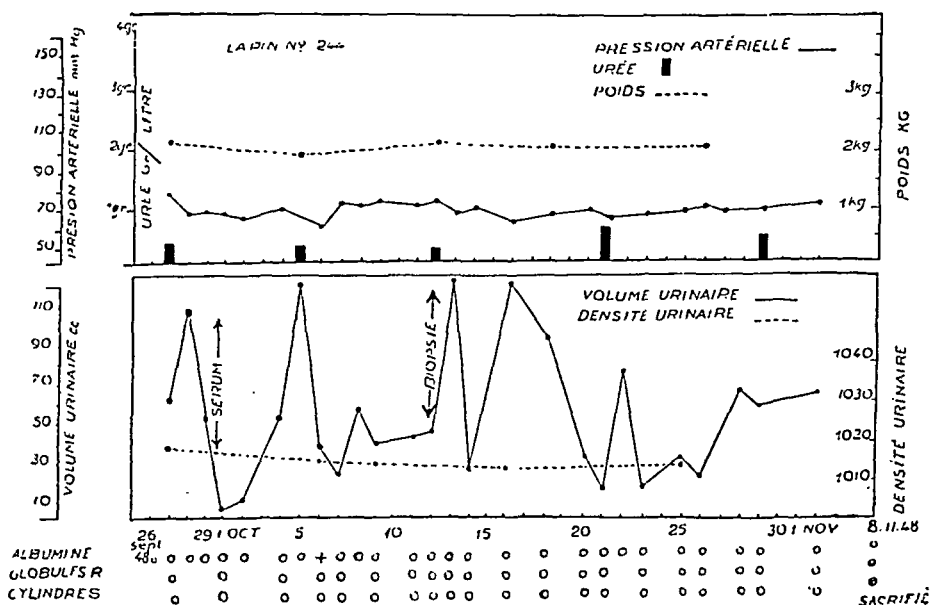


Figure 33.

Rein prélevé après sacrifice de l'animal : intumescence très discrète de quelques lobules floculaires au niveau de certains glomérules. Prolifération endothéliale extrêmement discrète également au niveau de quelques rares glomérules. Présence exceptionnelle de débris dans les lumières capsulaires. La plupart des glomérules ne contiennent qu'un nombre très limité d'hématies dans la lumière de leurs anses floculaires.

Pas de lésions épithéliales, présence exceptionnelle de cylindres constitués de débris dans la lumière des tubes.

Lapin N° 245 (fig. N° 34).

Evolution : Comparable en tous points aux deux cas précédents. Biopsie le 12^{ème} jour après l'injection de sérum.

Autopsie : Rein droit : 8,3 gr.

Aspect normal.

Histologie : Biopsie rénale : Très faible intumescence de tous les floculus

avec phénomènes plus ou moins marqués de prolifération endothéliale. Absence quasi complète d'hématies au niveau des anses floculaires de la plupart des glomérules. Ni substance albuminoïde, ni débris dans les lumières capsulaires.

On ne constate aucune lésion épithéliale. Les tubes ne contiennent aucun cylindre.

Rein prélevé après sacrifice de l'animal : intumescence relative d'un assez

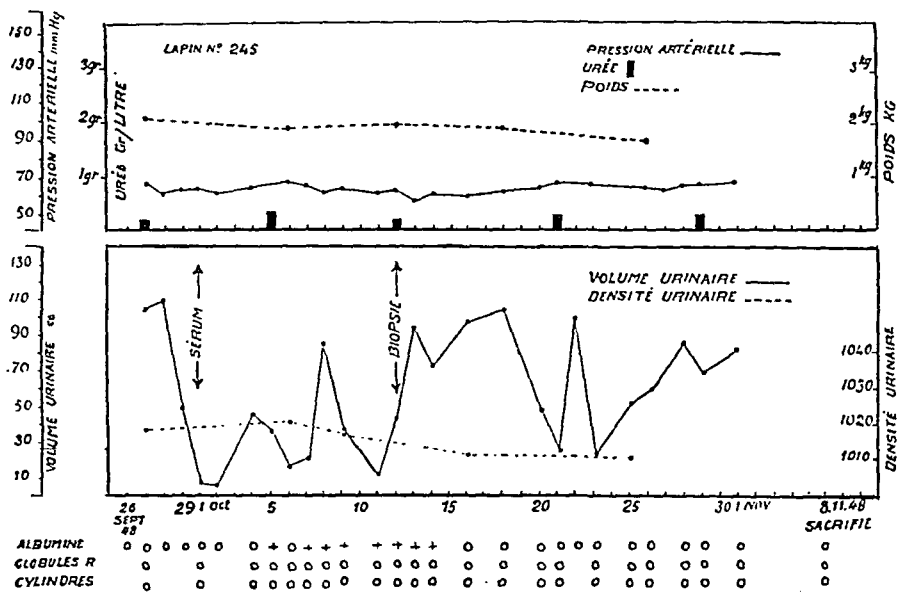


Figure 34.

grand nombre de floculus. Présence en quantité normale ou légèrement supérieure à la normale d'hématies dans les anses floculaires. Légers phénomènes de prolifération endothéliale au niveau d'un certain nombre de glomérules. Présence de débris en petit nombre dans la lumière capsulaire de quelques uns d'entre eux.

On ne constate pas de lésions épithéliales, mais un certain nombre de tubes contiennent dans leur lumière des cylindres constitués de débris.

Foie : Léger étalement fibreux des espaces portes.

Résumé : Nous voyons que l'injection d'un sérum de canard normal ne déclenche que des symptômes minimes : oligurie fugace, avec ou sans albuminurie transitoire ; cette réaction peut s'expliquer par le simple fait de l'injection d'albumines étrangères à l'animal.

Ces symptômes disparaissent rapidement et ne sont pas

accompagnés des autres signes urinaires rencontrés chez les animaux des lots précédents.

L'azotémie ne varie pratiquement pas, la pression artérielle n'accuse aucune élévation.

Du point de vue histologique, nous constatons toujours 1° : une certaine intumescence des flocculus, mais extrêmement discrète, 2° : une prolifération endothéliale des plus minimes à deux exceptions près, 3° : une anémie flocculaire peu marquée et uniforme sur l'ensemble des coupes.

On constate en revanche une absence quasi totale de substance albuminoïde dans les lumières capsulaires des glomérules ; la sclérose interstitielle, les lésions épithéliales et la présence de cylindres dans les tubes font également presque toujours défaut sur les coupes des reins de ces animaux.

En résumé, dans ce lot, seules les manifestations d'intumescence flocculaire et de prolifération endothéliale sont visibles, encore qu'elles soient considérablement réduites par rapport à celles que présentent les animaux des lots précédents.

DISCUSSION DES RESULTATS

1° — Il ressort de nos expériences, comme l'avaient déjà montré au demeurant plusieurs auteurs (8, 17, 18, 22, 26) que la gravité de la néphrite, tant du point de vue clinique qu'histologique est avant tout sous la dépendance du taux des anticorps antirein que contient le sérum de l'animal immunisé.

Il faut remarquer d'emblée que cette immunisation est absolument indépendante du procédé technique employé. Sur les six canards traités de la même façon, un seul présentait un taux élevé d'anticorps dans le sérum, un autre était moyennement chargé en anticorps, deux ne l'étaient que faiblement. Les deux derniers animaux, enfin, ne s'étaient pratiquement pas chargés en anticorps.

Il est donc absolument nécessaire de déterminer le taux des anticorps si l'on veut prévoir quelle sera l'intensité de la maladie. Ce dosage, vu la complexité du broyat injecté ne peut pas être d'une grande précision. De plus, les méthodes

employées sont diverses. *Il n'en reste pas moins vrai, que le taux des anticorps trouvé chez nos différents canards a provoqué des néphrites dont l'intensité a été rigoureusement proportionnelle à ces taux.*

Le mécanisme de la genèse de la néphrite expérimentale nous échappe encore. Si, pour *Masugi*, il s'agit avant tout d'un phénomène « d'allergie renversée », théorie qui a été confirmée par l'expérimentation (33, 34) et par la parenté morphologique lésions produites avec celles d'anaphylaxie locale et d'inflammation hyperergique décrites par *Rössle* (21), plusieurs chaînons de cette réaction complexe nous manquent encore, et il ne semble pas que le phénomène soit uniquement une réaction antigène-anticorps.

Suivant les procédés d'immunisation employés, les auteurs ont déclenché soit des lésions glomérulaires, soit des lésions tubulaires (*Castaigne & Rathery*) ou enfin les deux, avec une intensité sensiblement identique (17, 18, 26, 30, 32, 36, 37). Ces différences proviendraient essentiellement de la pureté des anticorps injectés.

Smadel fait une distinction entre la néphrose due à un sérum néphrotoxique pur (néphrose avec albuminurie, cylindrurie, azotémie, mais sans hématurie avec lésions tubulaires uniquement) et la « fausse néphrite » accompagnée, elle, d'hématurie avec lésions glomérulaires essentiellement et qui serait due à un choc anaphylactique. La première forme apparaîtrait quelques jours après l'injection de sérum, tandis que la seconde serait immédiatement consécutive à l'injection de sérum. Les deux formes pourraient se combiner dans la majorité des cas.

Derot (48) reprend dans son intéressante étude la discussion de ce problème et pense, qu'en clinique humaine, l'évolution par poussées de la néphrite résulterait d'une allergie vis à vis d'une toxine (streptotoxine par exemple) sur un organe préalablement sensibilisé à cette toxine, tandis que l'évolution chronique, à bas bruit serait le résultat de l'élaboration par l'organisme lui-même de néphrotoxines. Les deux formes peuvent évidemment s'enchevêtrer.

Kay, expérimentant sur des lapins auxquels il injecte du

sérum de canard chargé en anticorps antirein de lapin, en arrive à l'hypothèse suivante : il faut pour l'apparition de la néphrite que le lapin élabore tout d'abord des anticorps anti-sérum de canard qui réagissent avec le complexe « anticorps antirein-antigènes ».

A l'appui de sa théorie, il montre que des lapins qui ont reçu avant l'injection de sérum antirein de canard des injections de sérum normal de canard, font une néphrite beaucoup plus rapidement que les autres, qui ont déjà des anticorps anti-sérum de canard dans l'organisme. L'action des rayons X qui bloqueraient la copulation antigène-anticorps, empêcheraient l'apparition de la néphrite, si les lapins sont irradiés aussitôt après l'injection de sérum antirein.

Nous voyons par ces quelques faits que le problème de la genèse de la néphrite expérimentale est encore loin d'être résolu. Nous pouvons cependant tenir pour certain, qu'à l'origine de la maladie, la réaction « antigène-anticorps » joue un rôle primordial, mais que le développement et l'évolution de la néphrite obéit en plus à des causes encore obscures.

2° — Nous avons été frappés par la précocité de l'apparition des signes cliniques et des lésions histologiques. La plupart des auteurs indiquent un laps de temps variant entre quatre à huit jours entre l'injection de sérum et l'apparition de l'albuminurie, de l'hématurie, de la cylindrurie et de l'hypertension.

Chez les animaux du premier lot, l'action du sérum antirein a été quasi foudroyante. Elle a été plus discrète sur les animaux des lots 2 et 3. Enfin l'injection de sérum normal de canard n'a pratiquement pas causé de perturbations, tant du point de vue urinaire que tensionnel.

3° — La localisation et la spécificité des lésions est remarquable. Les reins sont pratiquement les seuls organes à être touchés. Les lésions minimales relevées au niveau du foie sont des plus discrètes. Les travaux antérieurs avaient déjà relevé la spécificité très grande sinon absolue du sérum néphrotoxique. (8, 15, 16, 17, 18, 32, 35).

Nous avons rencontré, au cours de nos expériences, des

lésions frappant essentiellement les glomérules. Les lésions tubulaires sont beaucoup plus discrètes et inconstantes. Leur intensité est en relation avec le taux d'anticorps des sérums injectés. Les signes cliniques ont été, eux aussi, en rapport avec le taux des anticorps. Notons en passant que l'élévation du taux de l'azotémie chez les animaux du premier lot, morts après 24 à 48 heures, nous ont frappé. La néphrite seule ne semble pas devoir en être responsable. Des phénomènes d'autolyse des organes ont du vraisemblablement s'y surajouter.

Du point de vue anatomo-pathologique :

a) Dans le premier lot d'animaux, l'intumescence des flocculus revêt une intensité tout à fait particulière sur les reins d'animaux morts dans les trois premiers jours. A partir du trentième jour, son intensité diminue considérablement.

Dans le deuxième lot, son intensité est sans rapport avec la durée de l'expérience. Dans l'ensemble elle demeure relativement forte.

Dans le troisième lot, l'intensité de l'intumescence diminue notablement. Elle se manifeste toutefois plus violemment chez les animaux morts ou sacrifiés plus tardivement (63 114 ou 180 Jours) que chez les animaux morts ou biopsiés dans les neuf premiers jours.

Dans le quatrième lot, à l'exception de trois préparations sur les dix sept étudiées, l'intumescence ne revêt qu'une allure tout à fait modérée par rapport aux lots précédents, sans qu'il n'y ait aucune relation entre son intensité et la durée de l'expérience.

b) Le phénomène de prolifération endothéliale présente une intensité sensiblement plus grande dans le premier lot, sans qu'il y ait un rapport strict entre celle-ci et la durée de l'expérience.

Dans le deuxième lot, l'intensité de ce phénomène est moins marquée que dans le premier, mais on peut noter qu'elle est maxima lorsque les délais d'expérience dépassent quatre vingt jours.

Dans le troisième lot, l'intensité de ce phénomène est sensiblement égale à celle qu'il présente dans le deuxième. Elle

arrive à un maximum lorsque les délais de l'expérience atteignent 180 jours.

Dans le quatrième lot, l'intensité de ce phénomène, a deux exceptions près (rein du lapin 239 prélevé au moment du sacrifice de l'animal et rein néphrectomisé du lapin 243) revêt une importance tout à fait négligeable par rapport à celle qu'il présente dans les trois premiers lots.

c) L'anémie floculaire est un phénomène difficile à apprécier sur l'ensemble de l'étude que nous avons faite, car, si sur certains reins elle s'étend à tous les glomérules, sur le plus grand nombre de préparations, elle ne s'étend qu'à une certaine quantité d'entre eux alors que les autres contiennent des hématies en nombre normal, voire même supérieur à la normale. Il est fréquent à ce sujet, d'observer le contraste qui existe sur un grand nombre de préparations, entre l'anémie des glomérules juxta-médullaires et la congestion des glomérules sous-capsulaires.

Dans le premier lot, le seul où ce phénomène revêt des caractères typiques et constants, on note que chez tous les animaux morts dans les trois premiers jours, les floculus ne contiennent aucune hématie. A partir du trentième jour, le nombre des hématies augmentent et cette transformation s'opère différemment suivant que l'animal a ou non été protégé. En effet, au-delà du trentième jour, chez l'animal protégé, le nombre des hématies est légèrement supérieur à la normale, tandis que chez l'animal non protégé, le nombre des hématies reste sensiblement inférieur à elle.

Dans le deuxième lot, les floculus contiennent pour la plupart un nombre sensiblement normal d'hématies.

Dans le troisième lot, nous faisons les mêmes constatations que dans le deuxième lot.

Dans le quatrième lot, le nombre des hématies est très notablement inférieur à la normale.

d) La présence de substance albuminoïde dans les lumières capsulaires des glomérules n'existe que sur les reins des lapins du premier lot, lorsque l'animal n'a pas survécu au-delà de trois jours. Un seul animal du deuxième lot fait

exception à cette règle (lapin 104, dont les glomérules contiennent dans leur lumière une quantité toutefois négligeable de cette substance).

e) La présence de débris dans les lumières capsulaires existe dans le premier lot, chaque fois que l'animal n'a pas survécu au-delà de trois jours. Un seul lapin fait exception à cette règle (rein prélevé au moment du sacrifice de l'animal 983, 210 jours après le début de l'expérience). La lumière capsulaire de ces glomérules contient des débris en très petite quantité toutefois.

Dans le deuxième lot, la présence de débris existe au niveau de tous les reins des lapins morts dans les 12 premiers jours à l'exception du lapin 107.

Dans le troisième lot la présence de débris est découverte cinq fois sans qu'il n'y ait aucun rapport entre elle et la durée de l'expérience.

Dans le quatrième lot, la présence de débris dans la lumière capsulaire présente avec une constance relative un caractère particulier qui est d'être le plus souvent retrouvée sur le rein restant de l'animal dont le rein nephrectomisé 15 ou 16 jours plus tôt en était dépourvu.

f) La sclérose interstitielle du glomérule est un phénomène exceptionnel et extrêmement discret lorsqu'il se manifeste. Dans le premier lot, on le rencontre une fois sur une biopsie faite au trentième jour (lapin 987). Cet animal avait été protégé par le phenergan, mais sa sclérose glomérulaire est beaucoup trop discrète et isolée pour qu'on puisse lui attribuer une réelle valeur.

On la rencontre une fois sur la deuxième biopsie d'un lapin du deuxième lot, faite au 88 jour (lapin 106). Il s'agit d'un animal protégé et les mêmes réserves s'imposent à son sujet qu'à celui du rein du lot précédent.

Par contre on le rencontre six fois sur les reins des lapins du troisième lot. Ce phénomène se manifeste cinq fois sur les reins de lapins morts ou sacrifiés au 180ème jour et une fois sur celui d'un lapin mort au 23ème jour.

g) Dans le premier lot, les lésions épithéliales ne se

manifestent que chez les animaux morts dans les 3 premiers jours. Dans le deuxième lot, elles ne se manifestent que chez les animaux morts dans les 24 premières heures. Dans le troisième lot, elles apparaissent de façon inconstante chez les animaux morts dans les 13 premiers jours. On les observe deux fois dans le cas d'animaux non protégés (1ère biopsie du lapin 909 et rein prélevé à la mort du lapin 906) et une seule fois dans le cas d'un animal protégé (lapin 903). Chez les animaux de 4ème lot, les lésions épithéliales font complètement défaut à l'exception d'un seul animal mort au 5ème jour (lapin 238) et d'un animal néphrectomisé au 12ème jour chez lequel elles revêtent d'ailleurs une intensité minime (lapin 244).

h) La présence de cylindres dans les tubes est contingente de celle de substance albuminoïde ou de débris dans la lumière capsulaire des glomérules.

Dans le premier lot, la présence de cylindres est contante sur toutes les préparations de reins dont les animaux sont morts dans les 3 premiers jours de l'expérience. Dans le deuxième lot, elle ne se voit que sur les reins d'animaux morts dans les 12 premiers jours d'expérience. Un seul cas fait exception à cette règle (lapin 105). Elle fait complètement défaut dans le 3ème et le 4ème lot.

Pour condenser ce que nous venous de décrire nous nous rappellerons que : dans le premier lot, on note au maximum l'existence de toutes les lésions élémentaires. L'intumescence des flocculus, l'anémie flocculaire, la présence de substances albuminoïde ou de débris dans la lumière capsulaire des glomérules, les lésions épithéliales et la présence de cylindres hématiques sont autant de phénomènes groupés qui s'avèrent d'autant plus manifestes que les délais d'expérience ont été plus courts. Seuls les phénomènes de prolifération endothéliale, plus intenses que dans aucun des autres lots ne subissent pas de modification en fonction du délai écoulé entre le début et la fin de l'expérience.

Dans le deuxième lot, seuls se manifestent avec une constance absolue les phénomènes d'intumescence et de prolifé-

ration endothéliale. L'intensité de ces derniers est nettement moins grande dans ce lot que dans le précédent. Par contre, ceux d'intumescence y conservent une intensité égale, mises à part les lésions épithéliales et la présence de cylindres hématisques dans la lumière des tubes, les autres manifestations sont tout à fait inconstantes.

Dans le troisième lot, les phénomènes d'intumescence floculaire présentent une intensité moindre que dans le lot précédent. Ceux de prolifération endothéliale y conservent une intensité sensiblement égale. Toutes les autres manifestations sont inconstantes dans leur apparition et dans leur intensité. Par contre, on note avec netteté, l'apparition tardive (à partir du 63ème jour) d'un léger remaniement interstitiel fibreux des glomérules.

Dans le quatrième lot, les seules manifestations relativement constantes se résument aux phénomènes d'intumescence floculaire et de prolifération endothéliale encore que leur intensité soit considérablement réduite par rapport à celle des lots précédents. Toutes les autres manifestations sont tout à fait négligeables.

Une vue d'ensemble nous permet donc de considérer

a) que l'intumescence floculaire comme les phénomènes de prolifération endothéliale n'appartiennent pas en propre à tel ou tel lot, et que seule leur intensité va en décroissant du lot 1 ou lot 4.

b) que la présence de substance albuminoïde comme celle de débris dans la lumière capsulaire des glomérules appartient en propre aux animaux du premier lot, lorsque les délais d'expérience n'ont pas excédé 3 jours.

c) que l'anémie floculaire ne présente de pureté véritable et de constance rigoureuse que chez les animaux du premier lot lorsque les délais d'expérience n'ont pas excédé 3 jours ; que le remaniement scléreux du glomérule appartient en propre aux animaux du 3ème lot lorsque les délais d'expérience ont excédé 63 jours et que, dans ces conditions, ce remaniement est deux fois plus fréquent chez les animaux non protégés que chez les animaux protégés.

d) que les lésions épithéliales appartiennent en propre aux animaux des lots 1 et 2, lorsque les délais d'expérience n'ont pas excédé 30 jours.

e) que la présence de cylindres hématiques dans la lumière des tubes appartient en propre aux lots 1 et 2 à condition que les délais d'expérience n'aient pas excédé 30 jours.

Les auteurs américains (54) ont décrit des lésions similaires, comme étant spécifiques de la glomérulo-néphrite, tant chez l'animal que chez l'homme.

4° — Sans pouvoir tirer de conclusions définitives sur l'évolution de la maladie, tant de point de vue clinique qu'histologique, nous pouvons cependant constater :

a) que chez les animaux des lots 1, 2 et 3 qui ont survécu un mois et plus, les symptômes urinaires tendent à s'amender et même à disparaître.

b) l'azotémie et l'hypertension, elles, ont tendance à persister, signant ainsi une atteinte rénale manifeste, bien que discrète.

Seuls les animaux du 3ème lot ont présenté de façon quasi constante des lésions de sclérose glomérulaire, faisant songer à une évolution vers la chronicité.

5° — A l'encontre des travaux de *Reubi* nous n'avons constaté aucune influence de l'antihistaminique de synthèse (phenergan) tant sur l'évolution clinique de la néphrite que sur les lésions histologiques.

L'un de nous (*Halpern*), a déjà attiré l'attention sur le fait que les antihistaminiques de synthèse semblent dépourvus de toute action dans les phénomènes allergiques où les anticorps sont supposés *intracellulaires* et au cours desquels la réaction antigène-anticorps aboutit surtout à des dommages intracellulaires. Dans les cas de néphrites allergiques, il s'agit d'une allergie inversée, où l'organe est l'antigène et où les anticorps sont apportés par voie circulatoire. Mais le résultat auquel on aboutit est le même et finalement, la réaction antigène-anticorps se produit à l'intérieur des cellules rénales. Cette absence d'action des antihistaminiques dans ces allergies « tissulaires » contraste avec les résultats remarquables qu'on

obtient avec ces corps dans les états où les anticorps demeurent dans les humeurs circulantes.

CONCLUSIONS GENERALES

1 — Nous avons créé chez le lapin un syndrome néphritique expérimental par l'injection d'un sérum antirein suivant la méthode de *Masugi*.

2 — Nous avons suivi au cours de ces néphrites l'évolution des signes urinaires, de l'azotémie, de la tension artérielle et des modifications anatomo-pathologiques.

3 — Nous avons constaté que la gravité des lésions dépend essentiellement du taux d'anticorps injectés.

4 — D'après la sévérité du syndrome et la durée de l'évolution des néphrites, nous les avons divisées en :

- a : suraigues,
- b : aigues,
- c : subaigues.

5 — Les néphrites suraigues sont caractérisées par une hématurie importante, une azotémie rapidement élevée, et des lésions anatomo-pathologiques très intenses : intumescence et anémie floculaires, présence de substance albuminoïde dans la lumière capsulaire, lésions épithéliales et présence de cylindres hématiques. La mort survient en général après 48 h.

6 — Au cours des néphrites aigues, d'allure moins dramatique, nous avons noté de l'hématurie, d'albuminurie, de l'azotémie et de l'hypertension. Les lésions anatomo-pathologiques ont les mêmes caractères mais sont moins intenses. Les phénomènes de prolifération endothéliale sont constants.

7 — Chez les animaux atteints de néphrite subaigue, on retrouve les mêmes symptômes que dans le groupe précédent, mais plus atténués. Certains animaux ont pu être suivis pendant 180 jours. Ici, les phénomènes de sclérose intersituelle deviennent un signe prédominant.

8 — Le traitement des animaux par un antihistaminique de synthèse très puissant, le phénergan, installé avant l'injection du sérum antirein et poursuivi pendant une longue période n'a pas change l'évolution ou la gravité du syndrome.



Planche XIII.

Vue d'ensemble des lésions obtenues chez un lapin du 2ème lot non protégé. —
Noter la forte intumescence des floculus associée à une forte prolifération endo-
théliale. Nombreuses lésions épithéliales cylindres granuleux et hématiques
(lapin 107 — mort dans les 24 premières heures — Bleu Masson).

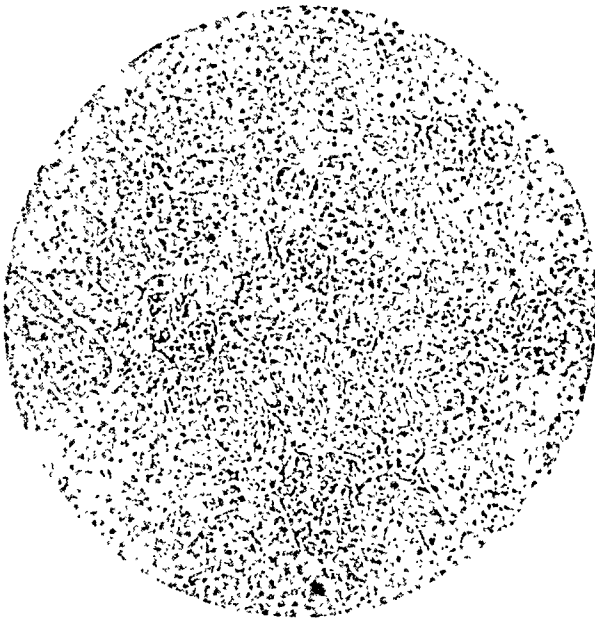


Planche XIV.

Vue d'ensemble des lésions obtenues chez un lapin du 2ème lot traité par le
phénergan. — Noter la très forte intumescence des floculus associée à une
prolifération endothéliale très notable. Pas de lésions épithéliales évidentes.
Noter qu'il n'existe pas ici d'anémie mais au contraire un faible degré de
congestion glomérulaire (lapin 103 — mort dans les 24 premières heures —
Bleu Masson).

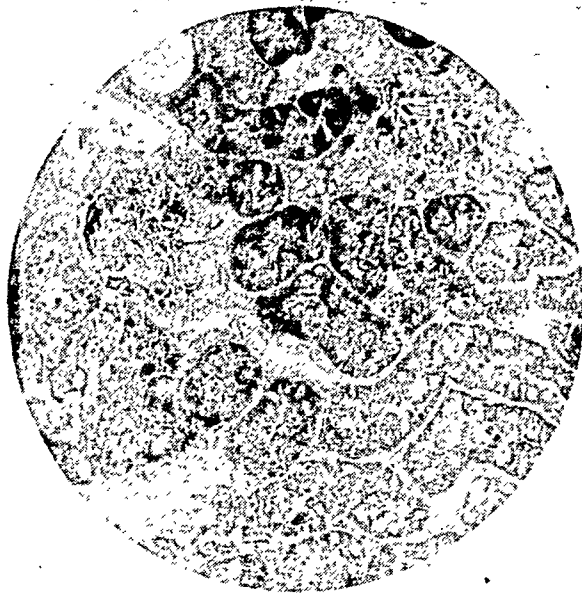


Planche XV.

Vue d'ensemble des lésions obtenues chez un lapin du 3ème lot non protégé. — Légère intumescence des foculus. — Très légère prolifération endothéliale pas d'anémie ni de congestion glomérulaire. Aucune lésions épithéliale (lapin 909 — biopsie au terme de 9 jours — Méthode d'Atmann-Volkonsky).

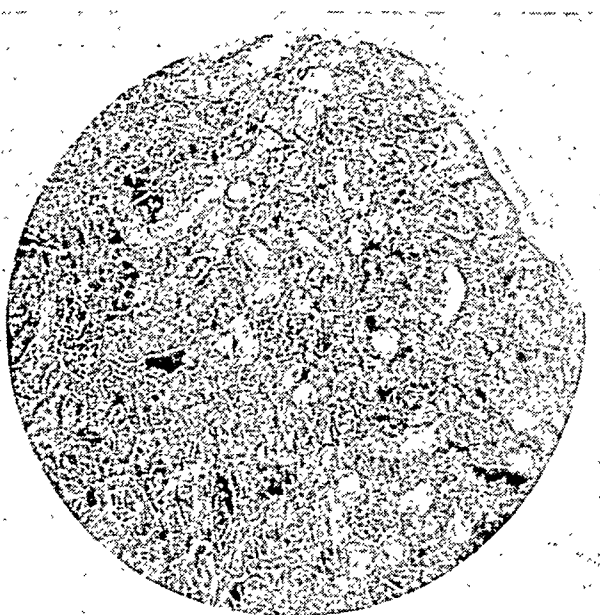


Planche XVI.

Vue d'ensemble des lésions obtenues chez un lapin du 3ème lot traité par le phénergan. — Très légère intumescence foculaire avec légère prolifération endothéliale. Quelques zones de dégénérescence graisseuses du tissu épithélial (lapin 903 — mort au terme de 5 jours — Bleu Masson).

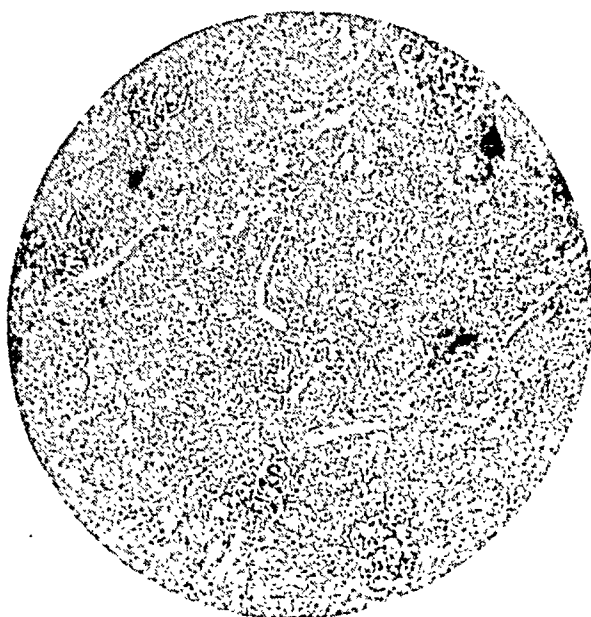


Planche XVII.

Vue d'ensemble des manifestations obtenues sur un lapin du 4ème lot (témoins).
 — Intumescence foculaire et prolifération endothéliale négligeables — pas
 d'altérations tubulaires — (lapin 244 néphrectomisé au terme de 12 jours —
 Bleu Masson).

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THE MECHANISM OF DESENSITIZATION WITH HISTAMINE

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The theory of histamine as one of the pathogenetic factors in allergic diseases is steadily advancing; consequently the histamine substances and histamine desensitization have become of great importance in the therapy of these diseases.

In a previous publication (Fabinyi and Szebehelyi 1948, a) we have already reported that we could desensitize white mice with histamine. We estimated the absence, respectively the reduction of the temperature-reducing effect of histamine as a sign of the resulting effect of the desensitization (Jancsó 1947). After histamine treatment for twelve days 3 mg histamine (which in normale caused a decrease in temperature of 3-4° C.) did not influence the temperature of the mice at all, and a decrease in temperature of 3-4° appeared only after the injection of 6-9 mg histamine. Consequently the histamine sensibility is reduced in desensitized animals. The temperature-reducing effect of histamine is due to an increase in the heat-deliberation caused by vasodilatation. As will be discussed in detail below, the temperature-reducing effect of histamine must be investigated at a temperature of 18-20° C. The progress of the desensitization can be observed step by step by measuring the variation of the temperature of the animals after the daily histamine injections. After twelve days' treatment with histamine, when the mice no more react to 3 mg histamine with a decrease in temperature, the temperature-reducing effect of other drugs (acetylcholine, doryl, or physostigmine) remains unchanged. Hence the desensitization with histamine proved to be specific in mice.

When examining the mechanism of desensitization with histamine our first question was whether the symptoms due to histamine are necessary to establish the desensitization, respectively whether the animal might get accustomed to the symptoms produced by histamine, or the symptom is of no importance and only the presence of the histamine molecule creates such a

process as results in protection. So we tried to desensitize without symptom. For 12 days we administered histamine to the mice, adding Pyribenzamine (N-pyridyl-N-benzyl-N-dimethyl-ethylendiamine: "Dehistin", prepared by Dr. K. Nádor at the laboratory of organic chemistry of our Institute) for the protection against the temperature-reducing effect of histamine. Pyribenzamine prevents the temperature-reducing effect of histamine. There is some difficulty in determining the dose of Pyribenzamine, as a great dose in itself reduces the temperature of mice. Two other groups of mice were given only histamine, respectively only Pyribenzamine, to serve as controls.

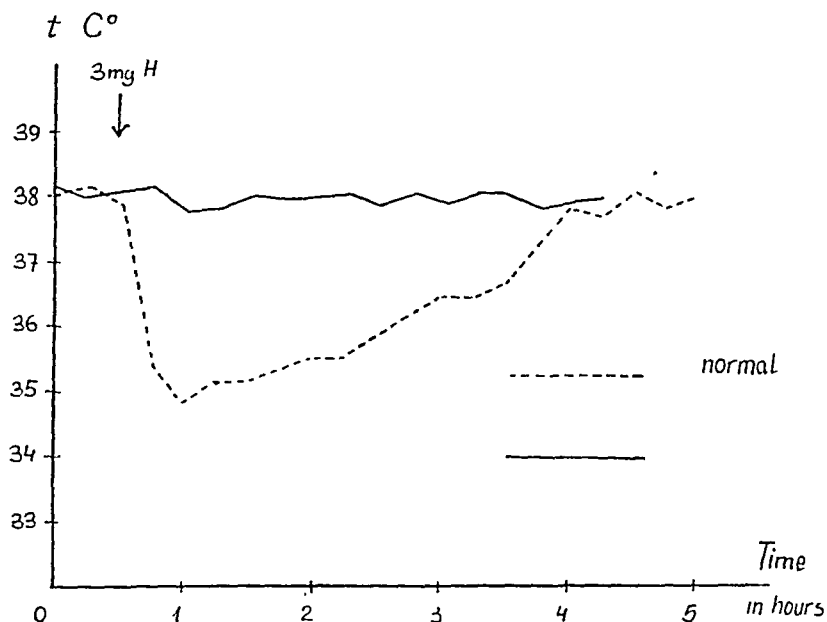


Fig. 1.

The first group (10 mice) during the first three days were given 2 mg histamine s.c. once a day, the next three days 3 mg histamine once a day, the following three 2 mg histamine twice a day, and finally the last three days 3 mg histamine s.c. twice a day. Whereas 3 mg histamine caused a decrease in temperature of $3-4^{\circ}\text{C}$. in normal mice, it did not change the temperature of the animals at all after a pretreatment with histamine for twelve days.

Besides the absence of the temperature-reducing effect of histamine we used another test to control the establishment of desensitization, viz. the rôle played by histamine in the increased rate of respiration due to lack of oxygen.

In a previous work (Fabinyi and Szebehelyi 1948, b) we have shown that an increase of the rate of respiration caused by the lack of oxygen, respectively by the inhalation of air containing 10 per cent. oxygen, did not ensue in mice desensitized with histamine. Consequently histamine—directly or indirectly—gives rise to an increase of the rate of respiration with lack of

oxygen. We shall not here discuss this question in more detail, but only refer to our observation according to which, if desensitization with histamine arises, the increase in the rate of respiration due to lack of oxygen ceases, to demonstrate once more the presence, respectively the absence of histamine desensitization. Fig. 2 shows the rate of respiration in normal mice and in mice desensitized with histamine after inhalation of air containing 20-16-14-12-10 per cent. oxygen.

The second group of 10 mice was treated with histamine in the same way as the first group, but 100 γ Pyribenzamine was given 30 min. before the

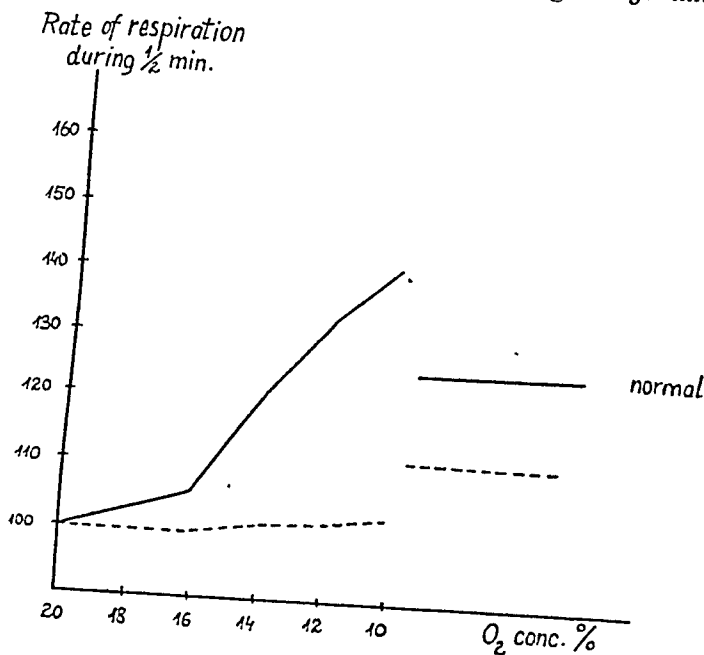


Fig. 2.

histamine injection and 50 γ Pyribenzamine together with it. This dose of Pyribenzamine protected the animals from the temperature-reducing effect of histamine without reducing the temperature itself. The third group of 10 mice were only given Pyribenzamine, the same doses as Group 2.

The mice treated with histamine and Pyribenzamine for twelve days (Group 2) did not react on the 13th day with a decrease in temperature after an injection of 3 mg histamine, whereas those mice which for twelve days were given only Pyribenzamine (Group 3) on the 13th day showed the same reaction to histamine (decrease in temperature) as those not treated at all (Fig. 3).

The fact that the animals treated with histamine and Pyribenzamine were actually desensitized also appeared from their behaviour when exposed to lack of oxygen: the respiration of the animals treated with Pyribenzamine only, showed the same increase when exposed to lack of oxygen as in those not treated; but the rate of respiration of mice treated with histamine and Pyri-

benzamine was not influenced by the inhalation of a gas-mixture containing 10 per cent. oxygen.

The same experiment was repeated with the difference that instead of Pyribenzamine adrenaline or atropine was given together with histamine. These drugs, although they do not influence the temperature-reducing effect of histamine, are nevertheless used in the therapy of allergic diseases and prevent some of the effects of histamine. Hence it was important to determine whether atropine and adrenaline might prevent desensitization or not. We found that none of these drugs influenced the desensitization with histamine.

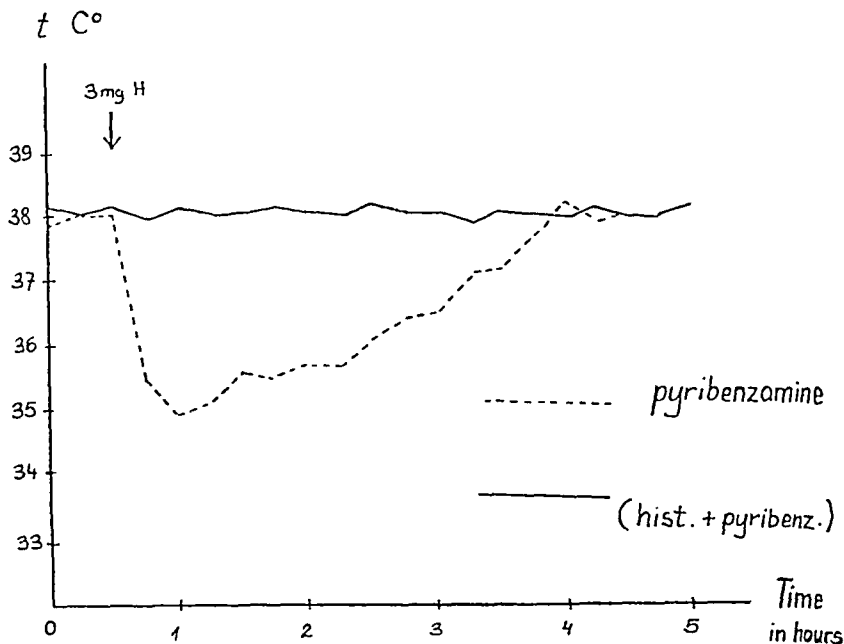


Fig. 3.

The fact that histamine desensitization can be established without developing symptoms caused by histamine allows us to penetrate into the mechanism of desensitization. Further the clinical importance of the question is evident from the fact that it is possible together with antihistamines to give allergic patients a higher dosis of histamine than needed for a successful desensitization—a dosis which would otherwise produce fairly grave symptoms in patients sensitive to histamine. The possible clinical importance of this question has been discussed elsewhere (Fabinyi and Szebehelyi 1949).

Accordingly we became aware of the fact that habituation to histamine ensued also when there were no symptoms. To account for this protection two possibilities must be considered: either the blood contains such a substance as is capable of destroying or neutralising histamine, or the cells reach a stage at which they react less to histamine. In the former case it may be assumed either that the activity of histaminase increases or that an antihistaminic sub-

stances arises, which then neutralises histamine chemically or in some other way, and circulates in the blood. According to experiments made by Went and Kesztyös (1946) histamine bound to albumen acts like a specific antigen, and blood from animals treated with such a histamine-antigen has an antihistamine effect. There is a possibility that histamine, which is not an antigen—being in itself a very small molecular substance—is bound in the organism to albumen like a hapten and thus produces antibodies. Further it should be noted that 10-14 days are needed to produce the desensitization.

To determine whether the habituation is of a humoral or a cellular kind,

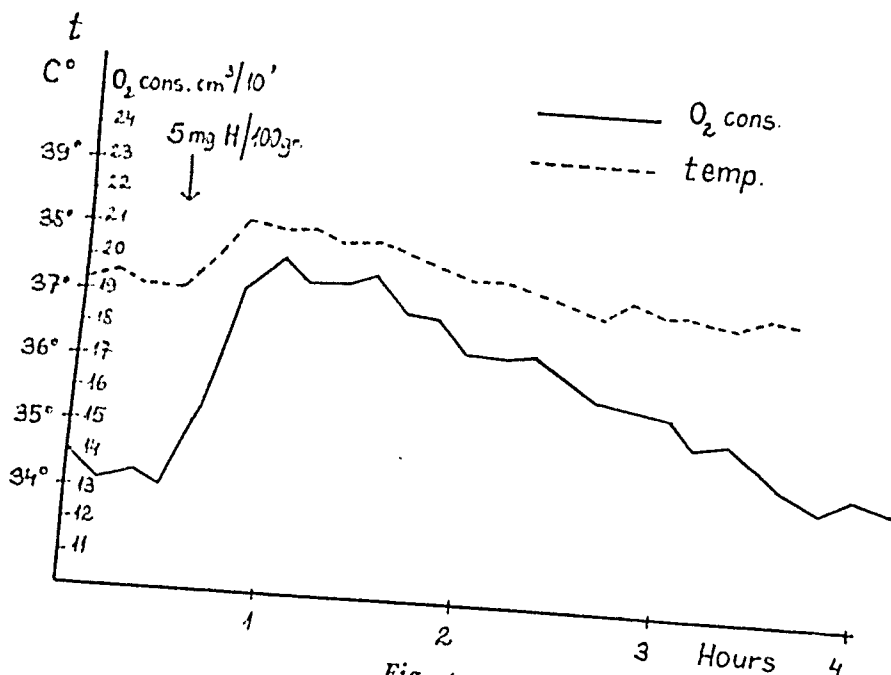


Fig. 4.

we started from the observation that desensitization does not neutralize every effect of histamine. If an antihistamine substance which would either bind or split histamine, were circulating in the blood then the absence of any effect of histamine was to be expected. The effect of histamine after desensitization with histamine is adrenalinaemia, due to excitation of the adrenals by histamine. This secondary adrenalinaemia was first observed by Dale in cats (1920).

Histamine increases the metabolism and temperature of mice and rats kept at 30° C. This is due to secondary adrenalinaemia. We shall elsewhere in detail discuss the method used in investigating this question (a modification of Issekutz's instrument for determining metabolism), and, further, the question why the temperature falls at 20° C. when there is no change in the metabolism, and the reason why it increases at 30° C. In connexion with our problem we have here only investigated the question whether desensitization

with histamine can prevent metabolic and the temperature-increasing effect of histamine at 30° C., i.e. the adrenalinaemia due to histamine.

Fig. 4 shows the effect of 8 mg/100 g histamine on the metabolism and temperature of rats at 30° C. The temperature and metabolism increased considerably.

This effect ceases after removal of the adrenals of the experimental animal, which was transfused with physiological NaCl and given per corten to keep it

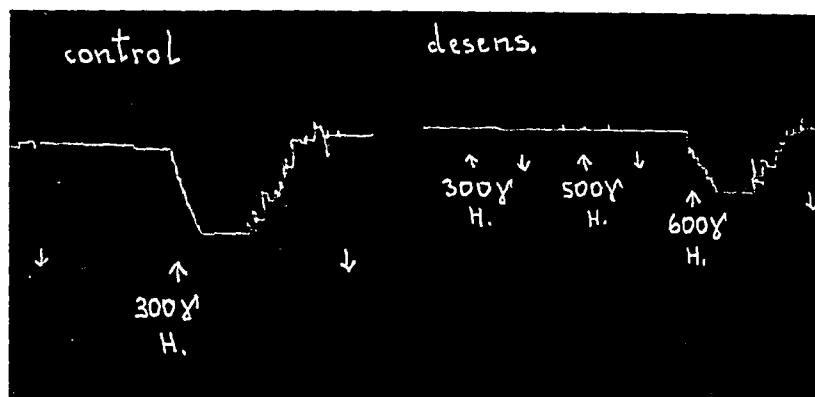


Fig. 5.

alive. But the histamine sensitivity of adrenalectomised animals increases enormously. The lethal dose of histamine in adrenalectomised cats became 12-62 times smaller than the original value given by Dale. In adrenalectomised rats it became 12.5 times smaller according to Crivellari (1927), and 20 times smaller according to Marmorston-Gottesman and Gottesman (1928).

In addition to these data we examined, in adrenalectomised cats, instead of 8 mg/100 g histamine, first the effect of 0.1-0.5 mg, then of 1-3 mg, finally of 5 mg/100 g histamine. None of these doses, however, produced any increase in temperature or metabolism, even 1 mg and higher doses of histamine reduced both, and 8 mg/100 g killed the animals.

Besides we investigated the question whether desensitization prevents the effect of histamine on metabolism and temperature at 30° C., i.e. whether it prevents the mobilisation of adrenaline. The desensitization of rats was performed in practically the same way as that of mice. For three days we gave 3 mg/100 g histamine s.c. once a day, then for three days 5 mg once a day, next for three days 3 mg twice a day, then for three days 5 mg twice a day, and finally for twice three days 8 mg/100 g histamine first once, then twice a day.

As in mice the absence of any temperature-reducing effect of histamine showed the establishment of desensitization. While 8 mg/100 g histamine reduced the temperature of normal rats by about 2-3° C., the same dose of

histamine after the eighteen days' pretreatment did not influence the temperature of the animals.

In rats desensitized in this manner we examined the effect of histamine on metabolism and temperature at 30° C., which effect depends on a compensatory adrenalinaemia, as pointed out above. As a result we may state that desensitization with histamine does not influence the metabolism- and temperature-in-

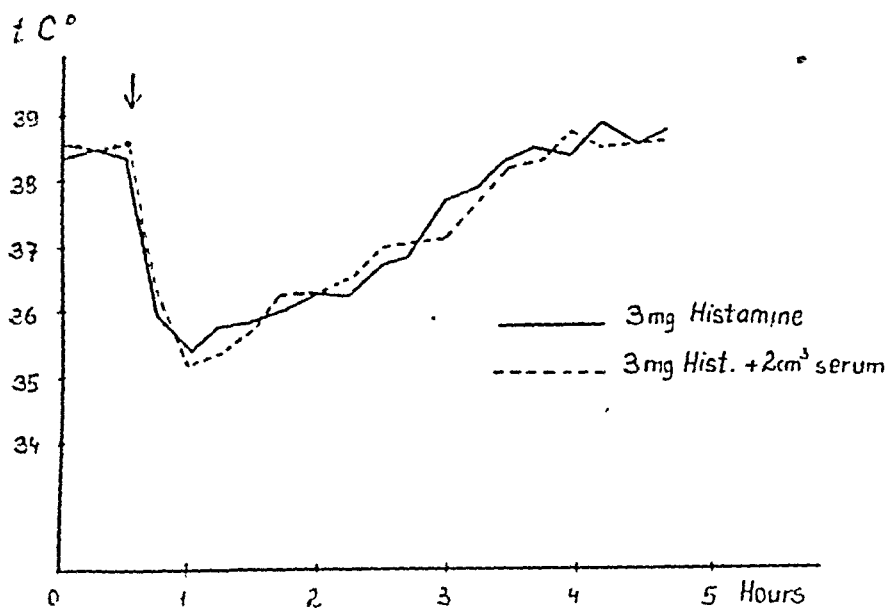


Fig. 6.

creasing effect of histamine at all, i.e. histamine at 30° C. increases the oxygen consumption and the temperature in desensitized rats, too.

This seems contradictory to the assumption that the blood should contain a kind of substance which decomposes or neutralises histamine, because, if so, the adrenal-stimulating effect of histamine would be absent.

On the other hand, in accordance with the cellular theory of histamine desensitization it can be explained why just the secondary adrenalinaemia cannot be absent, the reason being that histamine causes a marked hypertrophy of the adrenals. Consequently after a series of histamine injections an increase, but never a decrease, of the secondary adrenalinaemia would be expected.

We may get a direct answer to the question whether the essential feature of desensitization were a cellular or a humoral factor in two ways, viz. by examining *in vitro* the isolated and well-washed organs of desensitized animals and by examining the antihistaminic effect of the serum of desensitized animals.

It seemed most suitable to examine the isolated intestines of mice. Histamine produces a relaxation of the mice's intestines. This effect is one of the effects of histamine which is most difficult to prevent. For instance the synthetic

antihistamines may prevent this effect less than the gastric secretion-increasing effect of histamine.

According to the method of Magnus the well-washed isolated small intestines were immersed in Tyrode's solution at 37° C. 300 γ /ccm histamine causes a definite relaxation of the duodenum of the normal untreated mice. The duodenum of desensitized mice did not react to 300-500 γ /ccm histamine, and only with 600 γ /ccm histamine a similar relaxation was to be attained. 10 normal and 10 desensitized mice were examined (Fig. 5).

The cellular theory of histamine desensitization was proved in a series of negative experiments, too. We mixed the serum of desensitized rats with histamine and had it incubated for two hours at 37° C., and then examined whether the effect of histamine was reduced by such a treatment. Besides we gave the serum of desensitized rats to normal animals and examined the histamine sensitivity of these animals.

We incubated 2 ccm serum taken from desensitized rats with 3 mg histamine, and after injecting it in mice measured their rectal temperature. As shown in fig. 6, the serum of desensitized animals was unable to neutralize the incubated histamine, and the mice reacted to 3 mg histamine with an adequate decrease in temperature. To 10 mice we gave 3 mg histamine incubated in 2 ccm of 0.9 per cent. NaCl, and to 10 other mice the same quantity of histamine incubated in serum.

Afterwards, thirty minutes before the histamine injection, we gave 10 mice 2 ccm serum taken from desensitized rats, and then examined the temperature-reducing effect of 3 mg histamine. The result was that the serum given beforehand did not prevent the temperature-reducing effect of histamine. 2 ccm serum alone was without any influence on the temperature.

Experiments with guinea pigs gave similar negative results. We made normal guinea pigs inhale a vaporised solution of 0.2 per cent. histamine before and after the administration of serum obtained from desensitized rats. The average time needed for the appearance of the bronchial spasm remained unchanged.

It may be inferred from these experiments that during the desensitization there does not, in the serum, develop such a substance as would be responsible for the histamine resistance.

It might be objected to these experiments that the serum of sensitized animal may be unable to destroy, respectively to neutralize such a large quantity of histamine, as they do not correspond quantitatively to conditions of living animals. It may, however, be considered that e.g. a rat with a weight of 100 g only contains about 5 ccm serum.

During the desensitization such an animal will endure 8 mg histamine without symptoms; hence the relation between histamine and serum in our experiment has been to the advantage of serum.

Nevertheless we repeated the experiments with smaller doses of histamine. 5 γ histamine was incubated for two hours with $\frac{1}{4}$ ccm serum of mice at

37° C. We used the blood of 10 normal and 10 desensitized mice for the experiment. After the incubation the mixture of blood-histamine was shaken with an amount of absolute alcohol twenty times as large; afterwards the mixture was kept on ice for 6 hours, filtered, and evaporated at room temperature while air was blown through it.

The residue was then dissolved in a 5 ccm solution of physiological NaCl and the histamine content determined on atropinised cats by measuring the blood pressure. The serum had no histaminolytic effect either on normal or on desensitized animals. These results are in agreement with the results of Rose and Karády obtained from organs of rats. Only the lung and the small intestine showed a histaminolytic activity in normal animals. Even if the animals were treated for a prolonged time with histamine these two organs were the only ones showing any histaminolytic effect, and these observations, too, are in conformity with those found in normal animals. However, the authors did not control whether the histamine sensitivity of the animals decreased after the treatment. Still they gave such a large dose of histamine that at least a partial desensitization must ensue.

Besides, it seemed worth while to examine the question whether the intercellular substance (the collagen fibre) becomes resistant to histamine in the course of desensitization or not? In a previous paper (Fabinyi, Klein, and Szebehelyi 1948, c) we have already stated that 70 γ /ccm histamine induces a marked swelling of isolated collagen fibres in vitro. This swelling is proportional to the shortening; consequently the swelling can be expressed as the percentage ratio of the shortening to the original length of the fibre. These experiments were carried out for the maintenance of the histamine theory of inflammations, and in order to clear up the mechanism of action of the sodium salicylate therapy. We now examined the question whether the collagen fibre obtained from the tail of a desensitized rat swells at an adequate histamine concentration. The collagen fibre obtained from a normal rat's tail shortens on an average by 20 per cent. under the influence of 70 γ /ccm histamine. The collagen fibre obtained from the tail of a rat desensitized with histamine behaves similarly, histamine in that concentration producing a similar swelling.

Further we had to take into consideration that histamine causes a hypertrophy of the adrenals, and thus the adrenaline and cortine level might increase. Hence we examined the role played by the adrenals in the desensitization. Initially we investigated the problem whether the hormones of the adrenals prevented or reduced the effect of histamine, and further whether the desensitization with histamine can be established in adrenalectomised animals, too.

We have already observed that 0.2-1 γ /g adrenaline does not prevent or reduce the temperature-reducing effect of histamine in mice. These investigations were carried out with cortine, too, and the result was similarly negative:

after injection of 2-50 γ /g desoxycorticosteroneacetate (Doca) the temperature-reducing effect of histamine remained unchanged.

These results suggest that the adrenals do not play any rôle in the establishment of the desensitization. It cannot, however, be definitely proved by these experiments, for there is a possibility that the adrenals either produce some other substance with an antihistaminic property (e.g. some sterine), or in themselves (as organs) are capable of counter-balancing the effect of histamine independently of their secretions (Bomskov and Bakuren 1935).

To elucidate this question we tried to desensitize adrenalectomised mice with histamine. The difficulty, however, in this case was that the removal of the adrenals highly increased the histamine sensitivity of the animals (we have already in the previous part dealt with the data on this question found in the literature). We observed that whereas 3 mg histamine reduced the temperature of normal mice on an average by 3-4° C., the same dose of histamine caused a reduction of 8-10° in adrenalectomised mice. This effect was lethal in approximately half of the cases. When the mice were given 5 γ /g cortine in 1 ccm physiological salt solution daily and further 0.5 γ /g adrenaline twice a day, we observed a decrease of their sensitivity to histamine, a decrease which, however, did not reach the original value observed before the adrenalectomy, and 3 mg histamine reduced the temperature of these animals by 5-6° C. (It is a remarkable fact that in normal animals neither adrenaline nor cortine nor the physiological salt solution decreases the effect of histamine).

In order to compare adrenalectomised and normal mice as regards desensitization we had to bring the adrenalectomised animals into a condition where they could react to 3 mg histamine in the same way as the normal animals. However, we increased the doses of cortine and adrenaline in vain, the histamine sensitivity of the mice decreasing no further: hence they reacted to 3 mg histamine with a decrease of temperature of 5-6° C. However, it serves no purpose to compare the possible desensitization of such a kind of mice with normal ones in which the same dose of histamine reduces the temperature by only 3-4° C. We did not want to give them less histamine. Difficulties also arose from the fact that 3 mg histamine makes adrenalectomised mice collapse, the animals recovering only after several hours.

Hence our aim was to bring the adrenalectomised animals into a condition in which 3 mg histamine reduces the temperature—as in normal mice—by 3-4° C. only. This condition was obtained by administering 50 γ /g Pyribenzamine s.c. 30 minutes before the injection of histamine. This dose of anti-

histamine did not entirely prevent the temperature-reducing effect of histamine, but only reduced the decrease in temperature to $3-4^{\circ}$ C. Besides, the adrenalectomised animals reacted just as the normal control animals.

Consequently we had to begin with desensitization by means of the method reported. Pyribenzamine does not influence the development of the desensitization, as appeared from the previous experiments. Nevertheless, for the sake of control, we administered only Pyribenzamine to one group of adrenalectomised mice.

The first group of adrenalectomised mice always got Pyribenzamine before the injection of histamine. After 12 days' pretreatment, histamine + Pyribenzamine did not reduce the temperature of these animals; nor had 3 mg histamine without Pyribenzamine any effect upon the temperature.

The second—control—group of 10 adrenalectomised mice for 12 days was given only Pyribenzamine. After this pretreatment Pyribenzamine + histamine reduced their temperature by about $3-4^{\circ}$ C.

These results suggest that neither adrenaline nor cortine nor other sterines of the adrenals play any rôle in the establishment of histamine desensitization. Besides, it seemed worth while to examine whether cholesterol was not active in the desensitization. As is well-known, histamine gives rise to cholesterinaemia, though not in splenectomised animals, and on the other hand we know that cholesterol counterbalances certain effects of histamine. Hence we tried whether desensitization with histamine could be produced in splenectomised animals.

20 splenectomised mice were used for this experiment. The removal of the spleen did not influence their histamine sensitivity: 3 mg histamine caused a decrease in temperature of $3-4^{\circ}$ C. in a similar way as in normal mice. The desensitization was performed in accordance with the method reported. After 12 days' pretreatment with histamine 3 mg histamine did not reduce the temperature of these animals. This result shows that splenectomy—and hence probably cholesterinaemia due to histamine—does not influence the establishment of the desensitization.

It appeared from our experiments that cellular properties played a rôle in the desensitization with histamine. It is possible that the administration of histamine causes a continuous humoral change, which leads to a cellular alteration, through which the cells go into a histamine-refractory state—to be

more precise, the histamine sensitivity of the cells is reduced. A humoral change in itself does not explain the process of desensitization, for the serum has no antihistamine property.

Certain observations suggest that the alteration of cells during desensitization is the consequence of a change of permeability. Further investigations to elucidate this question are in progress.

S U M M A R Y

(1) Desensitization with histamine specifically reduces only histamine sensitivity in mice.

(2) The administration of Pyribenzamine does not prevent the establishment of histamine desensitization.

(3) The sensitivity to histamine of isolated intestines of desensitized mice is reduced.

(4) The serum of desensitized rats has no histaminolytic effect.

(5) The effect of histamine on the intercellular substance (collagen fibre) remains unchanged in desensitized animals.

(6) The hypertrophy of the adrenals plays no rôle in the establishment of histamine desensitization.

(7) Cholesterinaemia due to histamine does not influence desensitization.

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(Chief: Dr. A. Rothe-Meyer).

STUDIES ON MOSQUITO BITES

By

BJØRN HEILESEN

I. INTRODUCTION

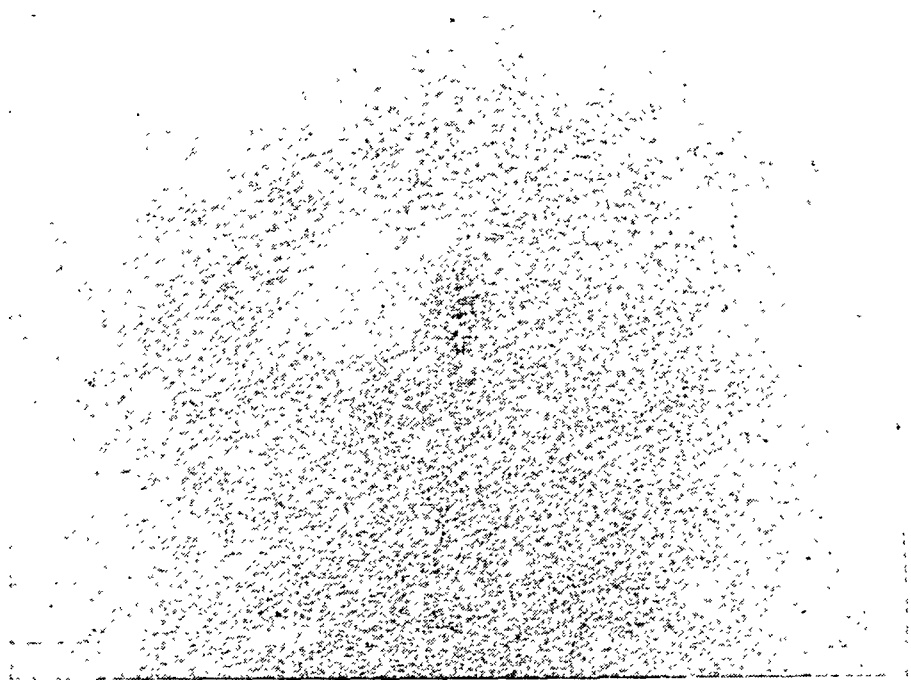
Because of individual qualitative as well as quantitative differences in the mode of reaction of man to mosquito bites, it has been generally assumed that mosquitoes have a special preference for certain individuals when they feed by sucking blood. *Gordon* (1922) and *Mellanby* (1946 b) have, however, shown by experiment that the mosquitoes attack all people indiscriminately if the experimental conditions are the same. The fact that some persons suffer particularly under the attacks of the mosquitoes must therefore be ascribed to peculiarities of the mode of reaction of these individuals.

The reactions of man to mosquito bites may manifest themselves in various manners. Either an immediate reaction may develop following the bite of the mosquito, consisting of a wheal and erythema, or the bite may be followed by a papular delayed reaction which will, as a rule, develop after 24 hours. The latter form of reaction may in exceptional cases assume the character of an Arthus phenomenon with necrosis (*Brown, Griffiths, Erwin & Dyrenforth, 1938, Culbertson, 1941*). Furthermore a peculiar flare-up of old sites following new bites of the same kind has been observed, the so-called "repetition reaction" (*Hase, 1944*). Finally, it should be mentioned that certain individuals do not react in any way after having been bitten by mosquitoes.

The immediate reaction is of the urticarial type, developing a few minutes after the bite, is transiently itching, reaching its maximum within 15 to 30 minutes, and subsiding within 30 to 60 minutes. The delayed reaction resembles a tuberculin reaction. It may persist for several days and is accom-

panied by a continual or intermittent itching. These reactions thus are analogous to the cutaneous reactions observed in allergic persons following intracutaneous injections of antigen to which these individuals have been sensitized; they have been characterized by *Sulzberger* (1940) as equivalent to these allergic reactions.

Biologists have for a long time attempted to explain the mechanism of the formation of a mosquito bite. *Cornwall & Patton* (1914-1915) thus mention



The figure shows the immediate reaction to *Aëdes aegypti* in a sensitized person (Exp. subj. No. 1) a few minutes after the bite (Magnif. \times abt. 4).

that *Lecurwenhoek* in 1695 tried to explain the bite in a purely mechanical manner while *Reaumur* in 1738 is said to have presumed that the irritation in the skin is produced by the insect secreting a toxic fluid into it. *Schaudinn* (1904), on the basis of the finding of yeast fungi in the oesophageal diverticula of the mosquitoes, developed the theory that the skin reaction was produced by irritation by Carbonic acid formed by the enzymes of these microorganisms, but *Cornwall & Patton* and *Roy* (1926-27) could not find yeasts in the digestive system of the mosquito. *Pawlowsky* (1929) tries to show experimentally that the salivary secretion is the direct cause of the skin reaction, whereas *Roy* and *Manalang* (1931) find that substances with the same irritating effect are found not only in the salivary glands but also in other organs, even if in lower concentrations.

Hecht (1929 a & b, 1930, 1933) by experiment with *Anopheles maculipennis* shows that the immediate reaction must be of an allergic nature, since it is possible, by means of a modified Prausnitz-Küstner technique, to demonstrate circulating antibodies to the secretion excreted by the mosquito while sucking blood. The experiment, however, was only successful in two subjects. Attempts to demonstrate antibodies in individuals with delayed reactions failed. Even so *Hecht* presumed that the delayed reaction also depended on a sensitization, since an individual who has first given a negative reaction, later produces a delayed reaction.

Mellanby (1946 a) has provided further experimental support for the view that mosquito bites are allergic reactions. In experiments on *Aedes aegypti* and *Anopheles maculipennis* this observer finds that persons who have not been previously exposed to the bites of these mosquitoes, only exhibit delayed reactions; after having been bitten repeatedly for a month they present immediate as well as delayed reactions. After repeated bites the delayed reaction later becomes less pronounced, or it may disappear completely. Also the immediate reaction may subside in persons who have been exposed to the bites of *Aedes aegypti* over a long period of time. *Mellanby* suggests that in the mode of reaction of man to mosquitoes we are concerned, first with an increasing sensitization (no reaction \rightarrow only delayed reaction \rightarrow immediate reaction and delayed reaction), followed by a desensitization (immediate reaction and delayed reaction \rightarrow only immediate reaction \rightarrow no reaction).

These observations are supported by other experimental and practical experience. The literature contains several reports showing that after being exposed to a species of mosquitoes by which they have not been previously bitten, human beings at first react very strongly, later on in a lesser degree or not at all (*Dawson Williams* (1896-97), *Morse* (1896-97), *Nuttall & Shipley* (1901-03), *Hase* (1916), *Gordon* (1922) and *Pawlowsky* (1927)). Similar observations have been reported in the case of *Phlebotomus* by *Newstead* (1911-12), *Doerr & Russ* (1913) and *Boycott* (1928). The last-mentioned author finds immediate as well as delayed reactions in a person who has been previously exposed to bites by *Phlebotomus*, while 4 unexposed persons gave no reactions at first to the bites of this species of mosquito, but at the end of 12 days exhibit a typical response. Also after repeated bites of fleas or *Cimex lectularius* the capacity of reaction of man may be altered. *Boycott* (1912-13), seems to be the first to have observed this phenomenon by experiment with *Xenopsylla cheopis* and *Ceratophyllus fasciatus* (rat fleas). By experiment with *Spilopsyllus cuniculi* (rabbit flea) *Boycott* (1926) also found a sensitization (after 7 days) and for later bites the reactions developed after a latent period of 36 hours. *Kemper* (1929 and 1930) works with bed bugs. In an experiment on himself he allows about 30 bed bugs to suck blood from the same area of the skin (measuring about 4 cm. in diameter) every three days or so for about 11 months. At first the latent period for the appearance of a skin reaction, which is described as an "urtica", is 24 hours; at the end of 4

months, the reaction appears immediately, and at the end of 8 or 9 months, the subject gives no reaction at all. This condition is not, however, permanent, since reaction reappears after an interval of 4 weeks in the experiment, and despite repeated bites this reaction persisted for some time. *Kemper* (1929) in another subject found a latent period first of 7 days, but after repeated bites over a year the latent period was reduced to three hours. *Hecht* (1930) found circulating antibodies in a person who gave an intense immediate reaction after bites by bed bugs.

These observations and experiments—especially those described by *Hecht* and *Mellanby*—thus suggest that insect bites may be of allergic nature, i.e., the result of a sensitization, but it is considered necessary to study the course of the sensitization in greater detail. It is also an open question whether all reactions to mosquito bites are allergic. In my own work I have attempted to produce an altered mode of reaction (possibly a sensitization) by means of repeated bites over long periods of time, to demonstrate the presence of antibodies in sensitized individuals, and, finally, to evaluate the immediate and delayed reactions observed as an expression for an existing sensitization. Finally, systematic attempts at desensitization will be of theoretical as well as practical interest.

II. THE EXAMINATIONS HERE PRESENTED

The experiments have been carried out partly at the London School of Hygiene & Tropical Medicine (department of entomology), partly at the Royal Veterinary and Agricultural College in Copenhagen (zoological laboratory), and partly at the Children's Hospital, Martinsvej, in Copenhagen.¹

In the experiments *Aedes aegypti* (A.a.) have been used, which have been hatched and stored according to the directions given by *Christophers* (1947). During the part of the

¹ I am greatly indebted to Professor *P. A. Buxton*, Dr. *K. Mellanby*, Professor *Mathias Thomsen* and Dr. *A. Rothe-Meyer*, chief physician, for excellent working conditions and valuable suggestions and advice in the performance of the work.

work carried out in Copenhagen, the bubbling of air in the vessels with larvae and pupae has been omitted, and the food used was a special kind of fish food and Becoplex. At 28°C and 80 % relative humidity the first pupa was seen—as also found by *Christophers*—after 6 days, and the first adult mosquito hatched after 7 or 8 days. Like *Atkin & Bacot* and *Christophers* the author has made the observation that clean tapwater is unsuited for hatching the eggs, which were therefore placed in water from a pond in the garden of the Veterinary and Agricultural College. Even though mosquitoes which had formerly sucked blood from human beings or guinea-pigs, produced the same reaction at repeated bites, the insects used were practically all female mosquitoes which had never previously sucked blood.

When the mosquitoes were to be used in experiments, they were carefully caught in a small cylindrical glass (5 cm. long, 2 cm. in diameter), the open end being covered with wide-meshed gauze which was fastened to the sides of the glass by means of adhesive plaster or paper sealing strips. When thereafter the open end of the glass was held against the skin, the mosquito would pass its proboscis down through a gauze mesh (abt. 1 mm.²). The glass was pressed firmly against the skin (unless otherwise stated, on the volar aspect of the forearm), until the mosquito had again withdrawn the proboscis. The resultant reactions, were measured in mm., first in the longitudinal direction of the arm, and then in the transvers direction. The mosquitoes generally fed for 2-5 minutes, only in exceptional cases from 5 to 10 minutes. The reactions were read immediately after removal of the glass, and further after 15 and 30 minutes. Unless expressly stated, "immediate reaction" in the following means the size of the skin reaction 30 minutes after the bite of the mosquito. In practically all the cases the reactions have been inspected at the end of 24 hours.

41 persons were used as experimental subjects (in the following called E.S.), one of these persons both in Copenhagen and in London (experiments carried out on the writer), 15

persons in London only and 25 persons in Copenhagen only. Of the latter, 10 were children, aged 6 months to 3 years, average 20 months. Of the adult subjects, 7 were women and 24 men, aged 18 to 55 years, the average age being about 30 years. A complete list of the experimental subjects is given in Table 1.

TABLE I
List of experimental subjects
(the number indicates age in years).

1. H. ♂ 34	11. A. ♂ 32	21. J. ♂ 20	31. W. ♂ 20
2. M. ♂ 39	12. J. ♂ 31	22. T. ♀ 41	32. W. ♂ 6 months
3. H. ♀ 32	13. W. ♂ 34	23. Å. ♀ 19	33. C. ♀ 16 months
4. S. ♂ 47	14. L. ♀ 30	24. H. ♂ 18	34. N. ♂ 14 months
5. L. ♂ 35	15. H. ♂ 37	25. A. ♂ 19	35. P. ♀ 13 months
6. C. ♂ 30	16. M. ♀ 20	26. M. ♀ 20	36. W. ♂ 2
7. L. ♂ 55	17. J. ♂ 45	27. J. ♂ 20	37. T. ♂ 1
8. B. ♂ 32	18. T. ♂ 51	28. C. ♂ 19	38. J. ♂ 18 months
9. W. ♂ 27	19. J. ♂ 19	29. H. ♂ 18	39. J. ♀ 2
10. M. ♀ 25	20. L. ♂ 40	30. F. ♂ 19	40. P. ♂ 3
			41. M. ♂ 15 months

Extracts were made either of mosquitoes which after having been killed with chloroform vapour had their wings and legs cut off, or of salivary glands which had been dissected out. The material was first placed in an exsiccator for 24 hours at 35° C., weighed and ground with powdered glass dust. After extraction with ether the non-lipoid remainder was suspended in physiological salt solution with 0.5 per cent. phenol, shaken for one hour and placed in an incubator for 48 hours. Next the supernatant fluid was pipetted off, filtered through a Seitz filter with a water jet pump and subjected to a sterility test. In extracts of whole mosquitoes the concentration was about 1/50. An amount of 0.1 cc. of the extract contains material corresponding to one mosquito. For the salivary extract, glands from 33 adult female mosquitoes were used (amount of extract 3.3 cc., i.e., 0.1 cc. of extract corresponds to the salivary glands of one mosquito).

B. *Experimental Results.*

1. *Experiments carried out on the Writer.*

The experiment started on May 13th, 1947. During the first 16 days the experimental subject (E.S. No. 1) was ex-

posed to 5 bites of A.a. daily. The subject had not been previously exposed to the bites of this species of mosquito which does not occur in northern Europe. During the first few days only small non-itching papules were seen 48 hours after the bite (abt. 3 mm.). On the 9th experimental day larger reactions appeared at the sites of two bites which were 48 hours old (measuring 8×8 and 13×13 in diameter), and on the 10th day reactions manifested themselves at 4 of the five sites of punctures which were 48 hours old (average size 13×12 mm.) and on the 11th day all five spots bitten reacted after 48 hours (12×12 mm.). Simultaneously with the development of these delayed reactions the subject felt an intense itching, which had not been the case after the bites during the first 8 days. After the 12th day the reactions declined quickly at the spots on which bites had been received 48 hours previously, and after the 17th day only small, not-itching papules were seen 48 hours after the bites.

On the 9th day, however, delayed reactions were also observed at the 24-hour sites of puncture where the reactions had formerly been negative. The delayed reaction after 24 hours on an average measured 7×8 mm. and were itching. On the 10th day the average measurement was 8×8 , on the 11th day 9×9 , and on the 12th day 12×13 mm. From the 12th to the 16th day the average of the daily 5 bites after 24 hours was 14×14 mm.

On the 15th day immediate reactions suddenly arose (wheal 7×6 mm., erythema 35×33 mm.) at the spots bitten: immediately after the mosquitoes had finished feeding these became the seat of intense itching.

From the 17th to the 58th day of the experiment the subject only had one bite daily (or, in some few cases, every two days). The delayed reaction after 24 hours from the 17th to the 40th day measured 10-20 mm., with an average of 14-15 mm. On the 42nd day the delayed reaction suddenly appeared after a latent period of only about 12 hours, and during the remaining part of the experimental period the latent period was gradually reduced to 8 or 9 hours, and

the reaction increased to 19-45 mm., the average size being 26×26 mm.

After an interruption of two months the experiment was resumed, one bite being administered every two days in the period September to November 1947 (105 days). During this period the immediate reaction consisted of a wheal measuring on an average 8×6 mm., and an erythema of 42×44 mm.

During this second experimental period the delayed reactions at first appeared after a latent period of 8 hours, but eventually at the end of only 2 or 3 hours. The average size of the delayed reaction was 15×15 mm. (8-25 mm.). Generally a small vesicle was observed at the site of puncture 24-48 hours after the bite.

Early as well as late reactions were accompanied by itching: the early reactions were of rather short duration, while the delayed reactions might itch rather intensely for a couple of days. Occasionally old bites would flare up when a new reaction to a bite developed in their vicinity or when the region was exposed to the influence of heat or friction. In experiments with bites on the thigh and abdomen the reactions were of approximately the same size as those observed on the forearms, except that the erythema was slightly larger.

The rather sudden reduction of the latent period on the 42nd day of the first experimental period occurred 8 days after injection with A.a. extract had been started; it will be dealt with in some detail later in this paper.

2. *Experimental Subjects who have been previously exposed.*

The exposure to bites by A.a. is designated as *intense* when the subject has been bitten many times over a long period of time, as of *medium* strength when the subject has only been exposed to bites for a fairly short time, and as *weak* if the subject has previously only been bitten a few times by A.a.

This group comprises 14 persons, 4 of whom have been intensely exposed (I), 5 submitted to exposure of medium

strength (II), while 5 persons have been only weakly exposed to bites by A.a. (III).

Of the 4 persons in group I, two presented no reaction (E.S. Nos. 4 and 15), while 2 displayed immediate reactions only (E.S. No. 5, wheal 5×5 , erythema 40×50 —E.S. No. 11, wheal 8×9 , erythema 40×50). Of the 5 persons in group II 3 exhibited immediate as well as delayed reactions (E.S. No. 2, wheal 6×5 , erythema 35×35 , delayed reaction (read at the end of 20 hours) 20×20 —E.S. No. 7, wheal 7×7 , erythema 40×50 , delayed reaction (read at the end of 24 hours) 20×20 —E.S. No. 16, wheal 10×10 , erythema 55×62 , delayed reaction (read at the end of 24 hours) 22×27 mm.) and 2 subjects only immediate reactions (E.S. No. 8, wheal 7×6 , erythema 50×70 —E.S. No. 12, wheal 12×6 , erythema 40×50 mm.).

Of the 5 persons who were weakly exposed (group III), 3 responded with immediate as well as delayed reactions (E.S. No. 6, wheal 8×5 , erythema 40×40 , delayed reaction (read at the end of 24 hours) 50×45 —E.S. No. 9, wheal 12×9 , erythema 35×40 , delayed reaction (at the end of 24 hours) 23×43 mm.—E.S. No. 14, wheal 18×7 , erythema 35×75 , delayed reaction (read at the end of 24 hours) 50×60 mm.; one responded with an immediate reaction alone (E.S. No. 10, wheal 4×5 , erythema 30×50 , and one with only a delayed reaction (E.S. No. 13, 9×7 mm., with a central vesicle).

The two subjects who had been intensely exposed and who gave no reaction (Nos. 4 and 15) were exposed to several experiments with bites. E.S. No. 4, who was a native of India and throughout his life had been exposed to "thousands of bites" received altogether 9 bites within 11 days, but it was not possible to alter his reaction. An experiment carried out 3 weeks later also gave a negative result. On the other hand, E.S. No. 15, who did not react to the first bite, developed weak, itching reactions to 2 bites on the 2nd experimental day (wheal 8×8 , erythema about 22×32 mm.). We are hardly concerned with any sensitization in this case, and this subject

should undoubtedly be included in the group of primarily occurring immediate reactions.

Attempts to procure immediate reactions in E.S. No. 13 by repeated bites over a period of 15 days failed. An urticarial wheal measuring 7×7 mm. was indeed observed on the 6th day, but there was no erythema and neither before, nor later did this subject exhibit the slightest indication of an immediate reaction.

A survey of these experiments is given in Table II.

TABLE II
14 adult experimental subjects previously exposed.

Reaction before experiment	Number	Exposed to repeated bites	Reaction altered By experiment
No reaction (absolute anergy)	1	1	0
Immediate reaction only	6		
Immediate & delayed reaction	6		
Delayed reaction only	1	1	0
No reaction (relative anergy)	0		

3. *Experimental Subjects who have not been previously exposed to A.a.*

a. *Adults.*

The experiments comprise 16 persons. 4 subjects (I) gave no reaction to the first bite, while a delayed reaction alone appeared in five persons (II), and 4 persons (III) only presented immediate reactions and three persons (IV) immediate as well as delayed reactions.

I. E.S. Nos. 3, 17, 20 and 24 gave negative reactions to the first bites. E.S. No. 3 was bitten once daily by one mosquito. The first two days only small palpules measuring a couple of mm. were in evidence, but on the third day a delayed reaction measuring 12×12 mm. appeared at the 48-hour site of puncture, and at the 24-hour site a reaction of 8×8 mm. After the experiment had been going on for 10 days the delayed reaction measured 15×17 at the end of 24 hours, and after 48 hours 10×10 mm., but there was no immediate reaction.

E.S. No. 17 presented on the 4th day (at the 2nd bite) an immediate reaction which it was possible to reproduce in the following four experiments, but a delayed reaction never appeared. The possibility cannot be ruled out that this subject had been exposed to bites of mosquitoes previously to the experiment, as he assisted the writer in hatching the mosquitoes. Therefore he should be left out of the material.

E.S. No. 20 was bitten every second day, and on the 17th day a delayed reaction developed at the end of 24 hours (8×10 mm.). The delayed reaction continued to be of the same size during the following two weeks, and there was no immediate reaction.

E.S. No. 24 was bitten every three days for 18 days and remained without reaction.

II. E.S. Nos. 21, 22, 26, 29, and 31 developed delayed reactions at the first bite. No more experiments were conducted on E.S. Nos. 22 and 26. In E.S. Nos. 21 and 31 continued bites produced an immediate reaction. The delayed reaction in E.S. No. 21 measured 10×7 , increasing till it measured 33×29 on the 12th day (with a vesicle 3 mm. in diameter centrally). The immediate reaction in this subject appeared after 4 exposures and on the 12th day. The wheal measured 8×8 , the erythema 30×30 mm., 13 days later a similar reaction was observed (wheal 5×6 , erythema 28×28). In E.S. No. 31 the delayed reaction at first was 10×10 and attained approximately this size during the remaining part of the experiment. The immediate reaction appeared on the 18th day and at the 7th exposure. The wheal measured 6×5 , and the erythema 25×20 . An experiment on the following day gave approximately the same reaction.

E.S. No. 29 was bitten 8 times within 24 days, in the course of which time the delayed reaction increased from 10×10 to 25×15 mm., but no immediate reaction appeared.

III. E.S. Nos. 18, 19, 27, and 30 at once exhibited immediate reactions (average size of wheal 8×7 , of erythema 34×43).

IV. E.S. Nos. 23, 25, and 28 at once presented immediate reactions as well as delayed reactions. In E.S. Nos. 23 the wheal (after 15 minutes) measured 18×14 mm., the erythema 40×50 mm., the delayed reaction (after 24 hours) 60×40 mm.; in E.S. No. 25 the wheal was 8×7 mm., the erythema 50×50 , the delayed reaction (after 24 hours) 30×30 mm., and in E.S. No. 28 the wheal (after 15 minutes) was 5×6 and the erythema 35×40 while the delayed reaction was somewhat varying at four exposures (in two experiments from 2 to 4 mm., in the other two experiments 8×11 and 12×12 mm. respectively).

E.S. Nos. 23 and 28 were allergic persons (previous urticaria, bronchial asthma and allergic eczema). The other subjects had not previously suffered from allergic conditions and could give no information about any predisposition. All reactions and results of experiments in this group are given in table III.

TABLE III

15 adult experimental subjects not previously exposed.

Reaction before experiment	Number	Exposed to repeated bites	Reaction altered by experiment	Reaction after experiment
No reaction (absolute anergy)	0			0
Immediate reaction only	4			4
Immediate & delayed reaction	3			5
Delayed reaction only	5	3	2	5
No reaction (relative anergy)	3	3	2	1

b. Children.

None of the ten Danish children aged 6 months to 3 years (average age 18 months) presented any reaction to the first bite, 4 of them were exposed to repeated bites, and all four gradually developed delayed reactions (cf. Nos. 32, 34, 35, and 36).

In E.S. No. 32 the reaction was observed for the first time on the 23rd day at a spot which had been bitten 24 hours previously (15×10 mm.). After 48 hours the reaction was 15×15 mm. The alteration in the skin's capacity to react appeared after 8 bites. In E.S. No. 34 a reaction measuring 7×8 mm. was seen on the 9th day at the 48-hour site of puncture, and a papule, 3×4 mm., with a central vesicle at the 24-hour site. During the following days delayed reactions kept appearing after 24 hours, but nothing could be seen at the site of puncture immediately after the bite. The delayed reaction at first increased in size 24 to 48 hours following the bite, but from the 14th day it attained its maximum size within 16 to 24 hours following the bite. The size on the 14th day was 13×15 , on the 16th day 16×17 and on the 23rd to the 24th day 22×15 mm. The positive reaction appeared after 6 exposures. In E.S. No. 35 reaction measuring 5×5 mm. appeared on the 6th day at the 48-hour site of puncture, and on the 7th day a reaction (25×25 mm.) at the 24-hour site. The positive reaction appeared after 4 exposures.

E.S. No. 36 suddenly exhibited a delayed reaction (8×8 mm.) at a 24-hour site on the 14th day of the experiment. The reaction could be reproduced in an experiment 2 days later (6 mm.).

4. *Experiments with Extracts of A.a.*

8 persons who had formerly been exposed to bites of *A.a.* were given intracutaneous injections of 0.1 cc of whole-mosquito extract made along the lines previously mentioned in this paper. The experiment includes E.S. Nos. 2, 4, 6, 10, 13, 14, 15, and 16. Only in one person, viz. E.S. No. 15, a positive reaction was observed, the wheal increasing from 6×5 to 11×10 mm., the erythema measuring 20 mm.; the reaction itched the first 10 minutes, and there were distinct pseudopods. In all the other persons the intracutaneous test had a negative result. Attempts to demonstrate circulating antibodies in E.S. No. 15 by means of Prausnitz-Küstner's technique failed.

Also in E.S. No. 1 a definitely positive, but weak intracutaneous reaction was demonstrated. The initial wheal was 7×6 mm. and without erythema. Within 20 minutes a typical immediate reaction with pseudopods (wheal 12×10 , erythema 30×25) developed, accompanied by a good deal of itching; after 24 hours a red infiltration (7×5 mm.) was in evidence. This result of the intracutaneous test could be reproduced. The initial wheal increased from 6×5 to 13×9 mm. within 30 minutes; the erythema was 25×35 mm., the infiltrate after 24 hours 15×15 , red and itching. Also with serum from this subject the Prausnitz-Küstner experiment gave a negative result.

Both of the two subjects who gave positive reactions must be considered to have been intensely exposed to *A.a.*, E.S. No. 15 having stayed for many years in tropical countries where the *A.a.* is found, while E.S. No. 1 had the intracutaneous tests done on the 30th and 50th days of the experiment.

Like the other subjects, E.S. Nos. 1 and 15 gave negative reactions to whole-mosquito extract from which the fat had not been removed with ether, and to salivary gland extract produced as described above.

5. *Experiments with Inoculation of Fresh Organs.*

Experiments with intracutaneous inoculation of crushed, fresh salivary glands or intestine gave varying results. Fresh salivary glands from one mosquito, crushed and suspended in physiological salt water with $\frac{1}{2}$ % phenol produced in E.S. No. 2 considerable swelling after about 24 hours. An area measuring 50×50 mm. surrounding the site of inoculation was red and itching. A central infiltration measuring 9×12

mm. was felt. Nothing was visible immediately following the inoculation. In contrast to this, salivary glands which had first been dried and thereafter suspended in physiological salt water with phenol, produced an "immediate reaction" which, 30 minutes after the inoculation consisted of a central area of the same size as the initial wheal (8×9 mm.) and an erythema of 30×50 mm. 24 hours later a central infiltration measuring 9×10 mm. was seen surrounded by an erythema of 40×60 mm. The reaction subsided within the next 24 hours. The same subject presented after inoculation of intestines, etc., an "immediate reaction" which after 30 minutes measured 20×20 mm., the central infiltration being of the same size as the initial wheal. 24 hours later it was 10×20 mm., and the erythema 40×40 . Control injections with physiological salt solution with $\frac{1}{2}$ % phenol alone gave negative results. The above mentioned "immediate reactions" had an urticarial appearance, while at the end of 24 hours a swelling was in evidence which was of an inflammatory type, red, itchnig intensely, often painful. These skin reactions bore no resemblance to the reactions following bites or the positive intracutaneous reactions obtained with extract of A.a.

III. DISCUSSION

A remarkable result of the studies here presented is the demonstration of an initial period without reaction (in the following called relative anergy period) followed by the appearance of a papular delayed reaction at continued exposure to the bites of the mosquito. This relative anergy period has formerly been observed by *Hecht* in an isolated case. *Mellanby's* subjects, on the other hand, all of them at once responded with a delayed reaction, and *Tezner* (1934) claims that practically all persons reacted to mosquito bites with swelling and erythema. In the experiments here recorded $\frac{4}{5}$ of the adult Danish persons who have never previously been bitten by A.a. at once exhibited delayed and/or immediate reaction (see Table III), whereas all ten children, aged

from abt. 6 months to 3 years, gave negative reactions, and in the four cases, in which the children were exposed to bites for some weeks, delayed reactions were produced after a period of from 6 to 23 days. *Tezner* (1934) stresses that *Hecht's* and *Kemper's* observations (see the introduction) are in favour of a view according to which the reactions of man to insect bites are comparable to the results of sensitization of human beings and other mammals by intracutaneous injections of foreign serum and ovalbumin. *Tezner* by experiments with ovalbumin (1934 a and b, 1935), found that after a relative anergy period of one week a delayed reaction, and one week later, also an immediate reaction set in. The former might disappear within 2 or 3 weeks, but in several cases it persisted unchanged. In some of the cases, but not in all, the immediate reactions also disappeared after continued intracutaneous injections of ovalbumin. By means of the Prausnitz-Küstner technique it was possible to demonstrate the presence of circulating antibodies.

If *Tezner's* observations are correlated with those of *Hecht*, *Mellanby* and my own, reported here, the resemblance of the form of reaction as to type and sequence is so striking that it would seem safe to presume that we are concerned with analogous processes. It is true that I have not been able to demonstrate the presence of circulating antibodies, as *Hecht* has done, but it is a well-known fact that the failure to demonstrate antibodies does not rule out the possibility of a sensitization: it is possible that the antibodies against the antigens in the salivary secretions of the mosquito may be present only in the skin.

The certainly weak, but definitely specific positive intracutaneous reactions which I observed in 2 subjects following injection of extract of A.a., also support the view that these individuals have become sensitized to A.a.

The fact that abt. 80 per cent. of the adult individuals who have never previously been exposed to the bites of A.a. respond with a delayed and/or immediate reaction, however, calls for a more detailed discussion of the question of the

allergic nature of the mosquito bites. This observation seems to support the presumption that the reaction of the human being to the bites of mosquitoes involves a primary toxic (possibly urticariogenic) influence. It is a well-known fact that intracutaneous injection of any fluid may elicit an immediate as well as a delayed reaction in the skin by a physical or chemical irritation (*Tezner*, 1935). Taking into account the infinitely small amount of fluid which the mosquito secretes when biting, a physical influence may presumably be left out of account. It is not possible, however, a priori to rule out the possibility of a primary toxic irritation by the saliva of *A.a.*, but it is rather unlikely that such a toxic irritant really does exist.

First of all, the possibility can hardly be excluded that the above mentioned Danish subjects who reacted to the first bite, may have been previously sensitized, e.g., by having been bitten by Danish mosquitoes. All Danish Culicidae are bloodsucking (*Wesenberg-Lund*, 1920-21). Species of *Aedes* occur among them and they frequently bite man. If, therefore, a person has not been out of Denmark or England he will not have been bitten by *A.a.*, but he will probably have been bitten many times by very closely related species. Antigens partaking of the character of haptens may possibly be of significance in this connection.

The question of the specificity of the sensitization produced by the mosquitoes has yet to be determined. Subject No. 2 reacted to bites of *A.a.* with an immediate as well as a delayed reaction, but gave a negative reaction to bites of *A. albopictus*, E.S. No. 10 responded with immediate reaction to *A.a.* but was without reaction to *albopictus*, and E.S. No. 16 reacted to both species of *Aedes* with immediate as well as a delayed reactions. Also in E.S. No. 1 an immediate as well as a delayed reaction of identical intensity to these two species of mosquitoes was found on the 22nd day of experiment, but the subject had never previously been bitten by *Aedes albopictus*. At the same time this subject was without reaction to *Anopheles maculipennis*, *Culex molestus*

and Cimex. As will be seen, nothing definite as to the specificity of the sensitization can be concluded from the examinations here presented.

Secondly, if the view is insisted that the secretion of the mosquito has a primary toxic effect, it will indeed be difficult to explain that a number of the subjects give no reaction whatsoever to the first bite, but begin to react after a certain latent period. The experiments on children suggest strongly a sensitization. In this connection, it is of interest that *Sulzberger* (1940) should stress that "many extracts considered as primary irritants solely because of the high incidence of reactions produced in adults, when applied in identical concentrations and manner elicit no whealing whatsoever in normal infants". Applied to the observations here presented this view involves that the primary reactions in a number of the adult subjects need not offer any obstacle for a presumption taking the mosquito bites to be of allergic nature, since the children have given negative reactions, but in several cases by repeated exposures have become enabled to react in the same manner as adult persons. The primary reactions in adult individuals thus only become an expression for the degree of sensitization of these persons.

The experiments on sensitization which have been carried out by Hecht, Mellanby and in the studies here presented, will thus have to be taken as very essential arguments in favour of the view that the mode of reaction of man to mosquito bites depends on the degree of sensitization of the individual. In this connection it may be indicated that a comparison of Table II and III shows that the subjects in Table III are definitely less sensitized than the subjects in Table II, but it is seen that by experiments they have been brought to a higher degree of sensitization.

Respecting the type of and relation between the immediate and delayed reactions observed, it should be stated that the results of the examinations on these points are in keeping with the experiences from other allergic reactions. The delayed reaction is changed by repeated biting, while the immediate

reaction is difficult to influence. *Mellanby* has shown that the delayed reaction may disappear completely, and in the present examinations (E.S. No. 1) its latent period was shortened significantly. These observations are also in harmony with *Kemper's* experiments, about which *Tezner* (1934 a) said that one cannot help thinking of the alteration of an allergic delayed reaction into an immediate reaction, in the same manner as it has been observed in his own sensitization experiments with ovalbumin. Such a change-over from a delayed to an immediate reaction has also been described by *Marcussen* (1948) as far as the reaction to trichophytin is concerned. *Mellanby's* examination as well as the experiments here presented seem to suggest that the reactions following the bites of insects take a similar course.

While *Mellanby* observed that individuals by repeated exposure to mosquito bites may become entirely negative (absolute anergy), *Benson* (1936) by desensitization of patients to mosquito bites finds that delayed reactions may be caused to disappear while the immediate reaction persists. The latter finding is in keeping with the experiences from other forms of treatment with desensitization, but the possibility cannot be ruled out that there may be a difference between treatment with extracts and the effects of numerous, frequently repeated bites over long periods of time. As mentioned in the introduction, practical experience supports the view that man may become entirely immune to mosquito bites. Such an absolute anergy is also in evidence in E.S. No. 4, who is a native of India and has lived his whole life in places where he has been frequently exposed to bites of A.a.

The conclusions appears to be that, at least so far as the delayed reactions to mosquito bites are concerned, a specific desensitizing treatment should greatly reduce the inconvenience caused to the individual.

After this discussion of the theoretical aspects, some few observations may be set down.

The primary anergic period has been demonstrated in 7 cases (in E.S. Nos. 1, 3, 20, 32, 34, 35, and 36). Regard-

ing E.S. Nos. 1, 3, and 34 it has been stated previously that a simultaneous reaction is observed at the 48-hour and 24-hour sites of punctures on the day when the change sets in. In all 3 subjects the former reactions are the largest. The same findings are observed on the following days; my conclusion is that the latent period is 24 hours but that the reaction increases in size in the period 24 to 48 hours following the bite. In the experiments described, after a few days the reaction reached its maximum size about 24 hours after the bite.

The length of the primary anergic period is on an average 11-12 days. The period of time required to establish sensitization to the salivary secretion of the mosquitoes is thus of practically the same duration as in the case of sensitization to other antigens.

Immediate reaction was produced experimentally in E.S. Nos. 1, 21, and 31, the two latter of whom reacted primarily by a delayed reaction, while E.S. No. 1 had a relative anergy period of 8 to 9 days. The immediate reaction made its appearance 15, 12, and 18 days respectively (average 15 days) after the beginning of the experiments. It is thus possible that the sensitization period before the appearance of the immediate reaction is independent of the primary mode of reaction of the individual, but of course nothing definite can be concluded on the basis of such a small number of persons.

Attempts to produce immediate reactions failed in two cases (E.S. Nos. 13 and 29, who were bitten for 15 and 24 days respectively), while attempts to produce a delayed reaction in a primarily anergic subject only failed in one case (E.S. No. 24).

In the discussion of the latent period of the delayed reaction in E.S. No. 1, stress is put on the sudden reduction of this period observed about 8 days after the institution of a desensitizing treatment with A.a.-extract. Following injection of increasing doses of this extract administered superficially subcutaneously for three weeks, the latent period is only about 8 hours, and 2 months later the latent period is found to be of the same length. At the end of the 2nd series of experiments

the latent period is only 2-3 hours. While the delayed reaction increased very gradually in size during the first half of the experiment, it declined in the second half of the experimental period, but did not go below the level it had at the beginning of the first series. Thus the attempt to bring about a complete desensitization of E.S. No. 1 with regard to the delayed reaction did not succeed, but, as already mentioned, the experiment calls to mind *Kemper's* investigations and presumably illustrates a transition from the stage in which there was an immediate as well as a delayed reaction to the occurrence of only an immediate reaction following the bite.

Tezner (1935) found that allergic persons (and persons with an allergic predisposition) in sensitization experiments react with a primary immediate reaction, but that it is possible to elicit a delayed reaction in these persons later on. It is striking in this connection that of the three Danish persons who presented immediate as well as delayed reactions the two had a history of previous manifest allergy. The other subjects could state nothing about allergy.

Comparative studies on the effect of bites of A.a. and of Danish mosquitoes have not been carried out, and would probably be of very little value because of the lacking specificity previously mentioned. By questioning the Danish adult experimental subjects about the inconvenience caused to them by Danish mosquitoes it would seem that a parallelism exists between the degree of the capacity to react to A.a. and to Danish mosquitoes. 9 subjects with a primary anergic period or primary delayed reactions to A.a. have noticed slight or no reactions following bites of Danish mosquitoes, while 2 of 4 persons with primary immediate reactions complained of fairly considerable inconvenience from the latter. Finally, all three persons who responded to A.a. with immediate as well as delayed reactions stated that they were greatly inconvenienced by the bites of Danish mosquitoes.

It is of considerable interest, theoretical as well as practical, that the two positive cutaneous reactions were obtained by means of an ether-treated extract, while an extract of the

same concentration, but without ether-extraction of the fats always gave a negative reaction. After evaporation of the ether extract a thick fatty layer was in evidence. This result confirms the experience that the presence of large amounts of lipoids will inhibit the effect of the antigens present in the extract.

The experiments on inoculations of organs are difficult to evaluate, the sterility is hardly complete, the reactions ill-defined, of an inflammatory character. These reactions are hardly comparable to the very different, well-defined and constant skin reactions following bites or injection of extract.

Both *Sulzberger* (1940) and *Urbach* (1944) mention the bullous reaction which certain individuals, especially children, exhibit following bites of insects. In the present experiments vesicular reactions (formations of a vesicle centrally on the papular delayed reaction) were observed in 5 subjects (Nos. 1, 21, 34, and 35, who had all of them been sensitized experimentally, and in No. 7 who had been intensely exposed to the bites of A.a.). A comparison of the reactions produced in E.S. No. 16, partly by A.a. and partly by *Aedes albopictus*, showed a severe bullous reaction (bulla 5 mm., infiltration 20 mm.) to the latter mosquito, whereas the delayed reaction following bites of A.a. was exclusively papular (22×27 mm.). The immediate reaction to *A. albopictus* was weaker than to A.a. (wheal 6×6 and 10×10 respectively, erythema 25×25 and 62×55 mm. respectively). E.S. No. 16 was examined by means of extracts of the two species of mosquitoes but reacted negatively to both.

As regards the so-called "flare-up" reaction which was mentioned in the introduction, it should be noted that it was apparently observed in E.S. No. 1 but that the phenomenon was produced not only by the development of new bites but also by rubbing or the influence of heat on the skin in the vicinity of old bites. The "flare-up" phenomenon, therefore, can hardly, as far as mosquito bites are concerned, be adduced as an argument for the presence of a local specific sensitization of the sites of puncture.

CONCLUSION AND SUMMARY

Mosquito bites produce immediate and delayed reactions equivalent to those elicited by allergic intracutaneous tests. *Hecht's* and *Mellanby's* experimental studies support the view that the reactions of man to mosquito bites are due to a sensitization.

In the present experiments *Aedes aegypti* have been used. Experiments were made on the writer and 40 other persons, including 10 children. Repeated exposures and intracutaneous tests with extracts of mosquitoes have afforded further support for the theory of an allergic nature of the mosquito bites. The experiments also suggest the value of desensitizing therapy but only as far as the delayed reaction is concerned.

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ON THE PROVOCATIVE EFFECT OF SYNTHETIC ESTROGEN ON ERYTHEMA NODOSUM

Preliminary Report

By

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Helsingfors.

The aetiology of erythema nodosum is still obscure, but so much seems obvious, that there are several forms of provocation acting as pathogenetic factors.

- 1) Various infections, such as angina, influenza, scarlet fever etc.
- 2) The administration of specific allergens (tuberculin, trichophytin, Frei-antigen, streptococcus-antigen etc.).
- 3) Mechanical and physical factors, such as surgical intervention (e.g. on affected lymph glands), roentgen therapy, ultra-violet rays etc. Also cold, e.g. standing in ice cold water, may be considered as a provocative factor.
- 4) Chemotherapy. From earlier publications we know of iodine, bromine, salicylic acid, antipyrine, phenacetin, salvarsan and antimony. During the last few years sulfathiazole has aroused special attention.

However, the hormones also, especially the female sex hormones, somehow seem to be of importance. We know that erythema nodosum is incomparably more frequent in women than in men. The infrequency of the disorder in male adults is seen from the following Scandinavian statistics:

Mogensen 3.0 %, Skiöld 4.5 %, Rotnes 4.9 %, Löfgren 6.7 %, Ingebrigtsen 13.7 %, Mascher 14.3 % cases.
Among female patients the incidence is greatest during the

years following puberty; in male patients, however, in childhood. As regards children the females do not dominate to the same extent as with adults (*Comby*: 65.9 %, *Rantasalo*: 45 %, *Roosvall*: 59.2 % girls). At the onset of puberty there is a sudden change, a rise in the female, and a decline in the male curve (*Favour & Sosman, Löfgren a. o.*).

There are observations in the literature (*Behrend, Jarisch*) indicating that the onset of erythema nodosum in women has a predilection for the premenstrual phase of the cycle, that is when the estrogen curve stands highest. *Opel* has described erythema nodosum-like eruptions appearing as a recurring menstrual exanthem in a 39 year-old "arthritic" woman. The infiltrations were atypically localized, it is true, on the face, on the right arm and on the chest, but they were accompanied by arthritic troubles in the hands and fingers. A further case of erythema nodosum in connection with the menses is given by *Gucissaz*.

Barrat & Koutseff have recently described a case of phlyctenular keratoconjunctivitis noticed 3 times in a young girl. The onset of the ocular attack became manifest each time about 48 hours before the menses. Endocrinological examination revealed symptoms of a relative hyperfolliculinia and insufficiency of the corpora lutea. The case is of interest in this connection as erythema nodosum and phlyctenular keratoconjunctivitis may be imagined as etio-pathogenetically closely related conditions.

With these cases in mind one is rather surprised not to find estrogens and stilbestrol—as far as I can see—mentioned as provocative agents in cases of erythema nodosum.

I should like to draw attention to stilbestrol in the following case report:

Case 1, doctor's wife, born 1911.

Hereditarily nothing noteworthy. No tuberculosis. Used to be healthy. Menarche at the age of 13. Aged 17, in connection with an angina, the patient had, at the beginning of November, 1928, a violent outbreak of Erythema nodosum on the lower extremities, from the ankles up to the buttocks. Tem-

perature ad 39-40° C. No symptoms from the lungs. No roentgen picture was taken on this occasion. On examination 9 years later, in 1937, the hilar shadows were enlarged, but no visible parenchymal processes were found. The tuberculin reaction was positive.

No spontaneous recurrence of erythema nodosum. She married in 1943. No children. She consulted a gynecologist in Nov. 1946. Diagnosis: *Uterus unicollis et unicornis. Cornu rudimentarium l. dx. Sterilitas primaria. Retroversio et sinistropositio uteri*. Sedimentation rate 7 mm. She was operated on, Nov. 15, 1946 (*Exstirpatio corn. rud. l. dx. et Redressio uteri*).

Synthetic estrogens (post mens.) were prescribed. She began the medication in Feb., 1947, with *Oestilben forte*, 3 tablets 3 times daily, corresponding to a daily dose of 0.0045 g diethylidioxistilbene dipropionate. About 6 days after the beginning of the course she developed erythema nodosum-like reddish infiltrations on both legs accompanied by pain, swelling and a feeling of heaviness in the legs, with rise of temperature to 37.5° C. The medication was discontinued, and the eruption disappeared within a few days, showing characteristic color changes.

A month later, after the next menstruation, a new attempt with the same stilbestrol was made, and with the same result. About 5 or 6 days after the beginning of the course, she developed similar red infiltrations as well as swelling, pain and tenderness in the legs, and the course had to be discontinued. A slight rise of temperature was noticed this time also. The infiltrations disappeared after 2-3 days, leaving dark patches which took a further 4-5 days to disappear. A third attempt at taking the tablets had to be interrupted after two days because of erythema nodosum.

The following year (1948) a new attempt at hormone treatment was made, this time with *Di-menformon*-injections, which the patient tolerated without side-effects, only a few injections being given.

In May, 1949, stilbestrol (*Stilbol*-tablets Medica) was given as an experiment; on this occasion, however, only with at most 0.005 g daily during 5 days, (0.0023 g in all). Now, also, she had a feeling of tenderness, tension, and heaviness in the legs below the knees, gradually increasing during the course and promptly disappearing when the drug was discontinued. This time no erythema nodosum-like infiltrations were noticed, probably because of the very careful administration.

The general condition of the patient was very good. Sedimentation rate 4 mm, throat and lungs healthy. On the roentgen picture in May, 1949, the hilar shadows seemed to be almost normal, or, in any case, non-contributory.

This case led me to try the effect of stilbestrol in another case of erythema nodosum. As an experimental object I had a 40 year-old woman who had recently suffered from

erythema nodosum due to sulfathiazole treatment. As the result obtained was positive, a short description of this case, too, may be indicated.

Case 2, a worker's wife, born 1908.

The patient used to be healthy. She has had no angina, no polyarthritis, nor tuberculosis. Several years ago she suffered from adnexitis, but for a long time she has had no troubles. In 1941 she had epidemic hepatitis. No menstrual disturbances worth mentioning, yet menses were latterly somewhat scarce. She has never before had erythema nodosum. She has not, as a rule, used drugs. She contends, for instance, never before having taken sulfonamides.

She was hospitalized because of an impetiginous eczema on her hands with signs of lymphangitis, and had, on Feb. 15, 1949, sulfathiazole, 12 tablets daily. On Feb. 16th she developed erythema nodosum-like reddish infiltrations on the extensor side of the left forearm. One of the lesions was about 30 mm large, the others being smaller. The medication was continued till Feb. 19th, and then interrupted when the patient had had in all 25 g sulfathiazole. This time she showed small reddish nodules, 5-10 mm in size, also on her right elbow and on the right knee. They disappeared in a few days.

The temperature was normal, throat and lungs without fault. She had three carious teeth (several teeth were missing). Sedimentation rate 38 mm. WaR —, Kahn —.

In the middle of March, 1949, stilbestrol (Stilbol forte, Medica), 0.0005 g 3 times daily was prescribed. On March 20th, having taken 0.01 g in all, the patient developed the same erythema nodosum eruption as before on the left forearm. Now, too, one of the lesions was large, the others measuring only 5-10 mm. They disappeared in a couple of days without showing any distinct change of color. Roentgenography of the lungs showed no visible parenchymal changes. The hilar shadows, however, were slightly enlarged on both sides.

DISCUSSION

The first patient was a 37 year-old married woman who, in 1928, at the age of 17, had an outbreak of erythema nodosum in connection with angina. Roentgenography in 1937 showed no parenchymal changes in the lungs, but the hilar shadows were said to be bilaterally enlarged. Because of sterility she was given 3 courses of stilbestrol in 1947. Each course, however, had to be discontinued because the stilbestrol provoked an outbreak of erythema nodosum on the legs.

If we regard erythema nodosum as being a specific infection we may in this case assume that it has existed in a

latent form for about 20 years, becoming manifest by provocation with stilbestrol.

The second case was that of a 40 year-old woman who had had neither angina nor erythema nodosum. In connection with a sulfathiazole treatment of an impetiginous eczema she developed an erythema nodosum-like eruption on the second day of treatment. A month later I succeeded in provoking a recurrence of her erythema nodosum with stilbestrol. Provided that the patient's assertion of never having taken sulfonamides was true it is difficult to consider her sulfathiazole erythema nodosum as manifestation of a sensitization to sulfathiazole, the lesions having appeared on the 2nd day of the medication.

In both cases it was a question of synthetic estrogen. Consequently it can by no means be taken for granted that the outbreak of erythema nodosum really was provoked by an estrogen hormone factor. The synthetic estrogens, as is well known, provoke side-effects more easily than natural preparations.

Perhaps we have only to do here with a so called "drug eruption", and not with an "idiopathic" erythema nodosum. However, a great many scientists share the opinion that erythema nodosum due to drugs, e.g. sulfathiazole, cannot be strictly separated from erythema nodosum idiopathicum, either clinically or histologically. (*Greither, Keil, Löfgren, Miescher, Tachau* a.o.)

Löfgren says that "the exanthemas arising after the administration of certain types of drugs, which have been described as "toxic erythema nodosum", ought in point of fact to be interpreted as having an infectious origin, and that the medication has only played the part of a provoking agent". Like many other Scandinavian authors he regards erythema nodosum as a non-specific hyperergic condition which may arise in connection with a number of different infections. According to *Bergstrand* it is perhaps a hypersensitivity reaction of the anaphylactic type, and presumably due to the protein or the carbohydrate component in the bacillary body. *Greither* mentions the negative result of the epi-

cutaneous and intracutaneous skin test, the missing eosinophilia, the high sedimentation rate, the histological structure and the total clinical impression reminiscent of an acute infection as factors pointing against a drug allergy.

Accordingly the erythema nodosum-like drug eruptions also would be a question of an infectious process with a possible biotropic activation of hidden micro-organisms (biotropism—*Milian*). The thought of a latent virus infection, made manifest by different provocations in the same way as herpes simplex or herpes zoster, comes to the mind (comp. *Miescher*).

The outbreak of herpes simplex in women coincides in a considerable percentage of cases with the premenstrual phase of the cycle, i.e. synchronomous with high estrogen levels or may be changes in hormonal actions. According to old statistics by *Bergh* in Copenhagen, 644 out of 877 cases of progenital herpes were of menstrual origin. Erythema nodosum arising premenstrually or provoked by estrogens thus offers close points of contact with herpes menstrualis. The menstrual urticaria, on the other hand, must be interpreted as an allergic manifestation.

Certain other conditions occurring premenstrually, like the premenstrual recurring ecchymoses described by *Stiller*, *Wilhelm*, *Behrend* and others, may also be mentioned in this connection.

The mode of action of the hormones in all these cases is far from clear. Their influence on the vasomotor system with hyperemia and changes in the permeability of capillaries etc. may perhaps be regarded as a contributory factor. Experiments on animals as to the influence of estrogen on bacterial and virus infections have given partly contradictory results. According to *Sprunt* and *McDearman*, *Foley* and *Aycock*, and *von Haam* and *Rosenfeld* estrogen exerts a protective influence against acute infections caused by vaccinia virus, streptococcus and pneumococcus, respectively. *Lurie & al.* have found that estradiol dipropionate retarded the tuberculous process at the site of inoculation in the skin and to

a considerable degree suppressed its dissemination in the body. By contrast, the periodic administration of chorionic gonadotropin, which induced successive crops of corpora lutea in the ovary, uniformly enhanced the tuberculous process at the site of cutaneous inoculation, increased its dissemination, and aggravated the extent of the disease in the internal organs. They found further that estrogen reduced the inflammatory response of the skin to tuberculin in sensitized rabbits by virtue of the depressing effect of the hormone on the inflammatory irritability of the skin to bacterial irritants in general. *Aycock* and *Foley*, on the contrary, have stated enhancement of tuberculous infection in guinea pigs by steroid hormones.

Many interesting problems are still unsolved. Further investigations also into the possible relationship between estrogen and erythema nodosum are desirable.

S U M M A R Y

A short survey of the literature concerning premenstrual erythema nodosum is given, and the possible connection between sex hormones and erythema nodosum briefly discussed. The case of a 37 year-old woman is described, who on three occasions developed erythema nodosum in connection with stilbestrol treatment (Diethyldioxistilbene dipropionate). In another case, a woman, aged 40, who had recently suffered from erythema nodosum due to sulfathiazole, *Sonck* succeeded in provoking a recurrence with synthetic estrogen. Further investigations into the possible relationship between estrogen and erythema nodosum are desirable.

Z U S A M M E N F A S S U N G

Das Vorkommen von praemenstruellem Erythema nodosum und der eventuelle Zusammenhang zwischen Geschlechtshormonen und Erythema nodosum ist im Kurzen erörtert. *Sonck* beschreibt den Fall einer 37-jährigen Frau, die im Anschluss an Stilboestrolbehandlung bei drei Gelegenheiten einen Ausbruch von Erythema nodosum bekam. Bei einer

anderen Frau, die kurz vorher an Sulfathiazol-Erythema nodosum gelitten hatte, gelang es *Sonck* mit Stilboestrol ein Rezidiv hervorzurufen. Weitere Forschungen bezüglich dem eventuellen Zusammenhang zwischen oestrogenen Hormonen und Erythema nodosum sind wünschenswert.

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For further references see the monographs of
Löfgren and *Tachau*.

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Prof. F. G. Valdecasas)

EFFECT OF ANTIHISTAMINIC DRUGS ON THE SENSIBILITY OF THE SKELETAL MUSCLE TO ACETYLCHOLINE AND POTASSIUM

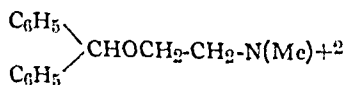
By

S. GLANZMANN, M.D. and J. A. SALVÁ, M.D., Ph.D.

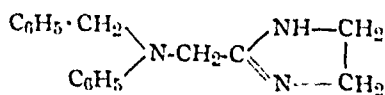
The behaviour of the various synthetic antihistaminic drugs with regard to different agents of muscular contraction has been studied by means of a great number of pharmacodynamic tests, all relating to the visceral or vascular smooth fibre, except those made in the special case of the cardiac muscle.

In order to contribute to the elucidation still necessary to the problem of the action of antihistaminic drugs on muscular activity, we have investigated the possible influences of these compounds on the response of the skeletal muscle to acetylcholine and potassium. These investigations have been started by one of us during a number of studies on antihistaminics.¹

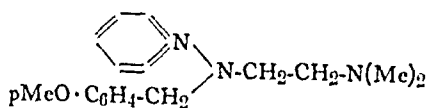
The following compounds were used in these experiments:



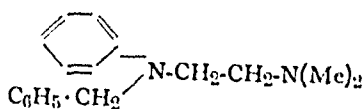
Benadryl



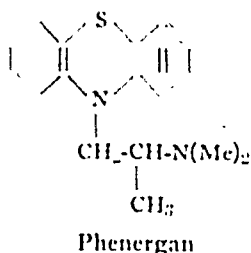
Antistine



Neoantergan



Pyribenzamine



Presumably the formulas of these five compounds represent the structure of the majority of the antihistaminic drugs used at present.

METHOD

The rectus abdominis of the frog was excised and after being kept in an ice-box for several hours was suspended in a muscle chamber of a capacity of 10 c.c. and filled with oxygenized Ringer (pH regulated at 7.2); isotonic record. Shortenings were induced at intervals of 10 minutes by replacing the Ringer of the bath with a 0.5×10^{-5} solution of acetylcholine in Ringer, which were left in contact with the muscle for a fixed time, usually 2 minutes.

In another series of experiments carried out under the same conditions, the contracting agent was a 0.2 per cent. solution of ClK in Ringer (derived from an isotonic solution of ClK).

Having obtained three similar responses, the muscle was exposed, once only, to the action of 100 gamma* of the tested antihistaminic during the last five minutes of the next interval (0.1 c.c. of a water solution being added to the washing liquid).

RESULTS

The antihistaminic compounds examined, in the doses used, reduce the muscular response, both to acetylcholine and potassium.

Though research is still in progress in order to establish an exact quantitative relation between the phenomena observed, some details can now be given of the variations observed with the different antihistaminic compounds.

* We have employed similar doses in weight of the different antihistaminics, the difference between their molar weights not being important enough to involve a notable error in the results.

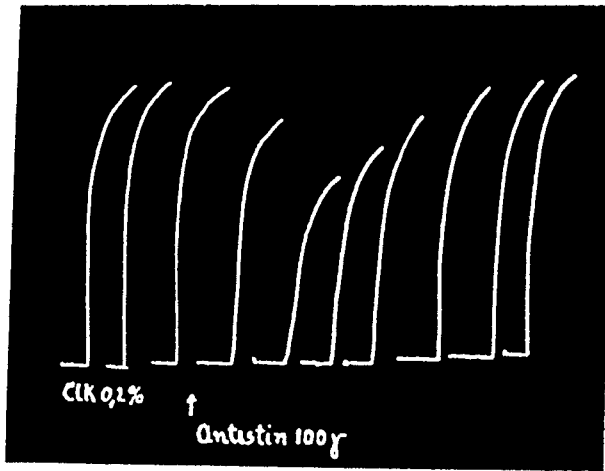


Fig. 1.

Antagonistic effect of 100 γ of Antistine on the responses of the frog's rectus abdominis to a 0.2 % KCl solution.

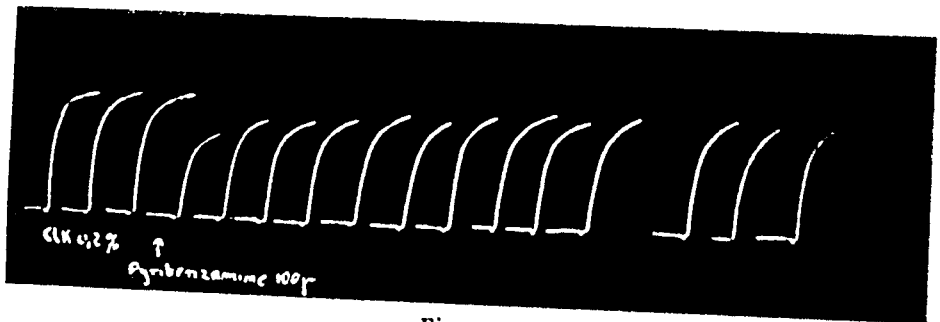
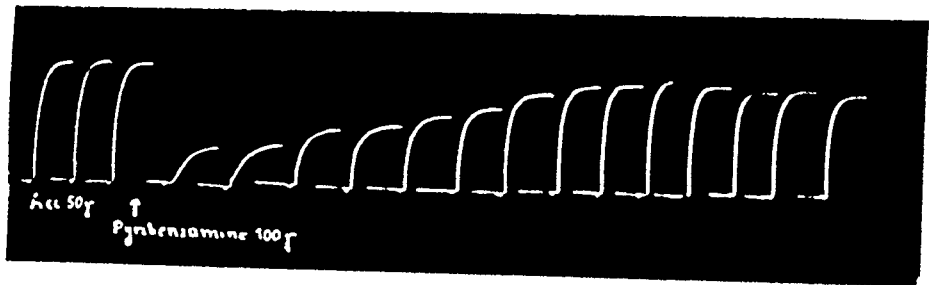


Fig. 2.

Antagonistic effect of 100 γ of Pyribenzamine on the responses of the frog's rectus abdominis to (I): 0.5×10^{-5} acetylcholine solution and to (II) a 0.2 % KCl solution.

The particulars noted for each compound, such as the time necessary for the maximum effect to appear, the per-

centage and length of the time of maximum recuperation and the shape of the recuperation curve coincide remarkably in both forms of contraction, the amount of maximum reduction, however, being considerably less for potassium.

Benadryl: The maximum reduction in the height of the

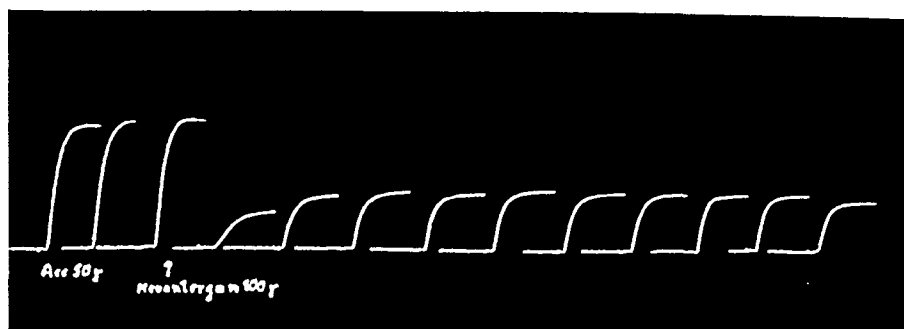


Fig. 3.

Antagonistic effect of 100 γ of Neoantergan on the responses of the frog's rectus abdominis to a 0.5×10^{-5} acetylcholine solution.

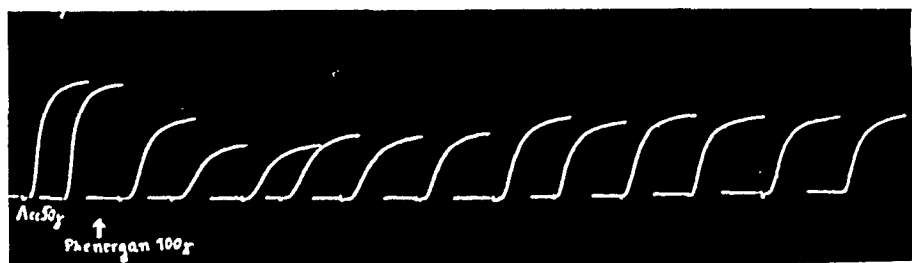


Fig. 4.

Antagonistic effect of 100 γ of Phenergan on the responses of the frog's rectus abdominis to a 0.5×10^{-5} acetylcholine solution.

curves is observed in the first response immediately after application of the antihistaminic. The recuperation is realized in lineal pregression, and completed in about an hour and a half.

Antistine: The maximum antagonist effect will not appear before the second response after the application of the antihistaminic (fig. 1). Recuperation is lineal and complete in about an hour.

Pyribenzamine: The maximum antagonistic effect is immediate and recuperation lineal (fig. 2). Both for acetylcholine and potassium the recuperation does not exceed 95 per cent. of the initial height of the contraction. This point is reached in one and a half hours in the first case and in one hour in the second.

Neoantergan: The maximum antagonistic effect is immediate. This initial reduction with sometimes a slight reduction in the second response, remains permanent and still persists 3 hours after the application of the antihistaminic (fig. 3).

Phenergan: A similar phenomenon to the one observed with Antistine is obtained, i.e. the maximum antagonistic effect does not set in until the second or third contraction following the application of the antihistaminic (fig. 4). Then a slight recuperation begins, which stabilises in about an hour without, however, surpassing 70 per cent. of the standard responses.

DISCUSSION

It is generally accepted that a comparison of the modifications produced by the action of a substance on the response of the striated muscle to acetylcholine and potassium, the effects of the latter being closely related to the mechanism of muscle contraction, furnishes good information on the influence of the substance upon the activity of striated muscle fibre.

The parallel of qualitative, and up to a certain point quantitative effects of the five antihistaminic compounds tested on the two forms of contracture allows of supposing a direct action of these drugs, with the doses used, on the excitability of the striated muscle.

SUMMARY

The modifying effect of various antihistaminic drugs on the contracture of the frog's rectus abdominis by acetylcholine and potassium has been studied.

All the antihistaminics antagonize both forms of muscular activation. The fixation of Neoantergan and Phenergan on the muscle is clearly superior to that of other compounds.

We wish to express our gratitude to Prof. F. G. Valdecasas for his assistance during the course of this work.

Thanks are due to Dr. B. N. Halpern, Paris, for Phenergan, Messrs. Ciba S.A. Barcelona for Antistine and Pyribenzamine, and to Messrs. Rhône-Poulenc, Barcelona for Neoantergan.

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ON FOOD ALLERGY AS THE CAUSE OF GASTRIC DISTRESS

By

PEKKA BRUMMER

As earlier shown by the writer in collaboration with Wegelius, it seems probable that disturbances in gastric motility form the immediate cause of gastric distress and that the case therefore is one of gastric dystonia and not of dyspepsia. The motility disturbance varies in type from one case to another, and different kinds of disturbance apparently may give rise to different gastric symptoms. Actual spastic conditions are thus probably the primary cause of severe attacks of gastric pain, whereas gastric atonia or functional retention may give rise to various sensations of indigestion.

In its relation to meals and various foodstuffs, gastric dystonia distress may be subdivided into two main types. With some persons the distress occurs after meals, quite independently of the kind of food ingested; with others it is present only after the ingestion of specific foodstuffs.

With persons in whom the type of food does not influence the distress, the symptoms, apparently, are caused by an unusually high irritability of the stomach, due to which the mechanical or chemical irritation brought about by the ingested food will readily cause disturbances in gastric motility. This irritability of the stomach is apparently based on functional and nervous instability. Organic gastric diseases, such as peptic ulcer and gastritis, may also produce or increase gastric irritability. However, as discussed by the writer in an earlier

paper, the part played by gastritis is probably not so great in this connection as is frequently presumed.

The etiology of distress is not so easily accounted for in such cases where the distress is caused by certain specific foodstuffs only. At least in North Finland, the most common foodstuffs producing gastric distress are meat, potatoes and milk, in the order of prevalence. It is difficult to understand why these specific foodstuffs produce mechanical or chemical irritation. True, the protein content of meat and milk might be regarded as of significance in this respect, for proteins are known to be fairly strong chemical irritants of the stomachs, as indicated by their stimulatory effect on gastric secretion. The potatoes, on the other hand, may be considered a fairly indifferent foodstuff in a chemical respect; nevertheless, as has already been said, it is, next to meat, the most general cause of gastric distress in North Finland, being in this respect very much more common than milk. It is furthermore fairly common that meat and potatoes cause gastric distress in the same person, whereas meat and milk do so comparatively rarely.

Earlier, when prevalent opinion connected gastric distress with secretory disturbances, the question why only certain foodstuffs give rise to distress in numerous patients was solved by the simple concept of difference in the type of secretory disturbance. The so-called achylia diets were later developed on this basis. These diets have been a source of great inconvenience to many patients and may sometimes have produced actual states of deficiency, while the relief obtained has probably been but little more than psychotherapeutic. One of the major foodstuffs to be avoided by persons with achlorhydria was milk. Now, on the contrary, it has been widely observed that milk can well be tolerated by many persons with achlorhydria, whereas it may give rise to distress in persons with hypersecretion. The ability of milk to produce gastric symptoms thus does not depend upon the gastric secretion. It may be mentioned in this connection that the writer, in making the study described below, found a case

which very clearly illustrates this point: a woman of 30 with hypersecretion suffered severe gastric distress after the ingestion of milk but not of buttermilk.

In seeking a reply to the question why the symptoms of so many gastric dystonia patients become manifest after the ingestion of certain foodstuffs only, attention is in the first place drawn to the possible share of food allergy. Many allergic persons have symptoms of various kinds referable to the digestive tracts. It can also frequently be demonstrated objectively that if such a person ingests a food allergen, the X-ray will show disturbances in gastric and intestinal motility which are more marked than those following the ingestion of other foodstuffs (Duke, Rowe, Fries and Zizmor, Fries and Mogil). Although, therefore, in many individual cases, and particularly where allergic persons are concerned, it is apparent that the gastro-intestinal symptoms which appear after the ingestion of a certain foodstuff are caused by food allergy, it is not certain that the same reason is applicable to the large class of gastric dystonia patients whose symptoms appear mainly or solely after the ingestion of the above mentioned common foodstuffs. On the contrary, the following points may be presented against the theory of allergic etiology:

- 1) It is the author's experience that the history of the latter patients very rarely discloses familial and past or present personal allergy. Allergy is by no means more common with these persons than with others.

- 2) Meat and potatoes are known to be considerably more rare food allergens than milk, yet they are a much more common cause of gastric symptoms.

- 3) With numerous persons in whom milk gives rise to distress, buttermilk does not do so. If the question were one of allergy, this difference would be hard to understand.

The following study was made for the purpose of obtaining further evidence either for or against the opinion that allergy is a factor in the etiology of the gastric distress felt by the numerous gastric dystonia patients in whom the above mentioned common foodstuffs produce distress. The study of

this question is greatly hampered by the lack of suitable methods of investigation. The negative evidence of the familial and personal histories has already been mentioned. Skin tests are not usually of much value in connection with food allergy, chiefly for two reasons, viz.: 1) Even if the skin test should indicate skin sensitization, this would not necessarily imply sensitization of the mucous membrane of the digestive tract; 2) The specific antigen is perhaps not the unaltered protein itself but some product of digestion, as demonstrated e.g. by Cole and Blamoutier. Vaughan's leucopenic index, which has been received with great interest, has by critical control studies been shown to be unusable for the recognition of food allergy (Loveless et al., Brown and Wadsworth). The literature has directed attention to changes not only in the total leucocyte count but also in the eosinophile count. Squier and Madison found that after the ingestion of allergenic food there occurs a constant increase of eosinophile cells in the circulating blood. This eosinophilia is not present if the foodstuff ingested is not one to which the patient is sensitive. The writer has been unable to find, in the subsequent literature, control studies on the occurrence and significance of digestive eosinophilia in food allergy.

Although the significance of digestive eosinophilia thus still remains unsolved, observations were made in the following study on the occurrence of digestive eosinophilia in gastric dystonia, particularly with persons who feel distress after the ingestion of the common foodstuffs referred to above, i.e. meat, potatoes and milk. The purpose was to cast further light upon the possible share of allergy in the etiology of this distress.

The tests and examinations were carried out on a material consisting of 54 persons, 15 of whom showed no gastric symptoms. The remaining 37 test subjects were gastric dystonia patients, in whom symptoms were manifest only following the ingestion of meat, potatoes or milk. The attacks of distress occurred after ingestion of one or, at most, two of the foodstuffs mentioned, in the latter case most commonly in con-

nection with meat and potatoes. None of the case histories revealed definite familial or personal allergy. On a part of the test subjects, examinations were made with all three foodstuffs, and on the remainder with one or two only. The first eosinophile count was made with an empty stomach; for the sake of comparison the total leucocyte count in the peripheral blood was also taken. The test subjects then ingested the food under investigation; 20, 40, and 60 minutes later, the eosinophile and total leucocyte counts were retaken.

The very first tests disclosed that no importance could be attached to variations in either the eosinophile or the total leucocyte count in the individual cases, as there were irregular fluctuations in both directions during the test, partly due to technical sources of error. For this reason no individual results are given in the following table, which lists only the mean values for each test group (Tables 1 and 2).

TABLE 1

Mean eosinophile and mean total leucocyte counts per cmm. after ingestion of meat, potatoes and meat, with persons who had no gastric dystonia symptoms, or in whom these foodstuffs produced no distress.

(Number of cases stated in parentheses).

	Meat (15)		Potatoes (19)		Milk (33)	
	Eosino- phile count	Total leucocyte count	Eosino- phile count	Total leucocyte count	Eosino- phile count	Total leucocyte count
Before ingestion	175	5300	170	4500	165	5800
20 min. after ingestion...	185	5300	165	4600	175	5800
40 " " " ...	170	5500	170	4600	170	5500
60 " " " ...	170	5300	175	4800	160	5600

As shown in the tables, no definite changes can be found in the mean eosinophile count or the mean total leucocyte count after ingestion of meat, potatoes or milk by persons in whom these foodstuffs produce gastric symptoms, or by persons in whom they do not produce such symptoms.

TABLE 2

Mean eosinophile and mean total leucocyte counts per cmm. after ingestion of meat, potatoes and milk, with persons in whom these foodstuffs produce gastric distress.

(Number of cases stated in parentheses).

	Meat (20)		Potatoes (17)		Milk (10)	
	Eosino- phile count	Total leucocyte count	Eosino- phile count	Total leucocyte count	Eosino- phile count	Total leucocyte count
Before ingestion	165	4600	165	5800	130	4800
20 min. after ingestion...	150	4500	160	5200	125	4900
40 " " " ...	145	4500	155	5500	135	4500
60 " " " ...	160	4600	155	5500	140	4400

If it can be regarded as a fact that the ingestion of an allergen tends to produce eosinophilia in a person with food allergy—which, in the writer's opinion, can be regarded as probable, although not definitely proved—the results obtained in the present study confirm the opinion already discussed above, that allergy is of at least no marked significance in the etiology of the gastric distress of those gastric dystonia patients with whom the distress is produced only after ingestion of the common foodstuffs studied.

SUMMARY

With numerous gastric dystonia patients the symptoms become manifest only after ingestion of certain common foodstuffs. At least in North Finland the most general of these foodstuffs are meat, potatoes and milk. The writer made observations to determine whether these foodstuffs can be found to produce digestive eosinophilia with persons in whom they produce gastric symptoms. No definite changes could be observed in the mean eosinophile count or in the mean total leucocyte count. The writer considers that this finding, together with certain other reasons which are pre-

sented, supports the opinion that allergy is of no great significance in the etiology of the gastric distress mentioned.

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ON LIPSTICK DERMATITIS

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In literature on the subject lipstick has already a couple of decades been mentioned as a cause of dermatitis. However, patch tests performed with the various ingredients of lipstick to determine the causative are not made very often.

Baer reported a case in which a synthetic ingredient of a perfume, methyl heptene carbonate, caused dermatitis. *Sulzberger, Goodman, Byrne & Mallozzi, and Feiler* etc. have also elicited positive reactions with perfume. However, the dermatitis is most often due to the dyes contained in the lipstick. Many authors have found eosin and certain other derivatives of fluorescein to be the cause of dermatitis (*Miller, & Taussig, Sézary, Horowitz, & Genet, Hallier, Flandin, Rabeau, & Ukrainczyk, Hecht, Rappaport & Bloch* and *Sulzberger & al.*). In some of the cases photosensitization was considered an additional factor (*Peck* etc.). In eight cases *Sulzberger & al.* showed a distinct hypersensitivity to certain azo dyes also (1-sulpho- β -naphthalene-azo- β -naphthol, a mixture of sodium salt of m-xylene-azo- β -naphthol-3,6-disulphonic acid and sodium salt of β -naphthalene-azo- β -naphthol-3,6-disulphonic-acid, p-nitro-benzene-azo- β -naphthol (para red, dark), para red, light, oil sudan). Ponceaurot (*Sielge & Co.*) to which *Putkonen* has demonstrated hypersensitivity in two cases also belongs to the azo-dyes. *Sézary, Horowitz & Genet* have presented cheilitis caused by tolusaphranine. In many cases it is impossible to find out the chemical formula of the dye in question, so one must be satisfied with the patented trade name, in so far as that can be traced. *Putkonen* reports having also determined hypersensitivity to "Gelb fettlöslich" (a mixture of different dyes, *Schimmel & Co.*) and "Lippenstiftorange R" (*Siegle & Co.*). *Schonberg* has reported a case in which dermatitis was occasioned by a liquid lip rouge, but he did not state the causing ingredient.

In Finland several cases of lipstick dermatitis due to sensitization to toluene-azo-toluene-azo- β -naphthol¹ have recently

¹ (= Sudan IV, is called TATAN in this paper).

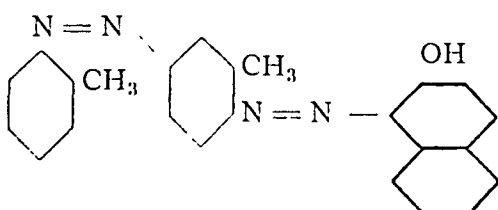


Fig. 1.

occurred. As, in so far as I am aware of the fact, no cases caused by this azo-dye have been discussed previously in the literature, I consider it justifiable to publish the cases I have discovered.

Material. During a period a little over 6 months (from autumn 1947 to summer 1948) a Finnish cosmetics factory received 5 complaints because lipstick manufactured by it had caused dermatitis. Two of the patients were treated at the Dermatological Clinic of Helsinki University where I had the opportunity of examining them thoroughly. One of the patients did not, in spite of requests, arrive for examination and two lived outside of Helsinki and could not thus be examined. About the same time two patients with lipstick dermatitis visited me privately. In one case a product of the said factory was the cause, and in the other the lipstick bore the Swedish trade mark "Mitzi". In this case a clear, although not very strong reaction, was elicited by a patch test made

with the lipstick itself. As information about the ingredients in the lipstick was not obtainable from the factory, the substance to which the patient was hypersensitive remained unsolved. In all the other cases a reaction was obtained with both the lipstick itself and TATAN. Also in the cases in which the patch tests were not performed the patients had applied lipstick, which contained TATAN in addition to various dyes and other ingredients. It seems very probable that dermatitis appeared in all the patients, who had developed it from the lipstick of the said factory (altogether 6 known cases) due to sensitization to TATAN.



Toluene-azo-toluene-azo- β -naphthol = Sudan IV.

Patch tests. In general, dyes used in the manufacture of lipstick are not primary irritants. Thus among other authors *Sulzberger* & al. used "pure colors, as commercially prepared" in patch tests without causing reactions in even one of the 25 control persons. The control tests performed with the dyes now in question (ca. 50 % in olive oil) also were all negative (10 persons). Apparently on selecting dyes for cosmetics attention has in general been paid to their possible irritating characteristic and an effort has at least been made to choose such dyes which are not primary irritants. However, exceptions may be met with. In the material of *Pulkonen* "Gelb fettlöslich" (Schimmel & Co.) produced a reaction also in some patients whose lipstick did not contain the said dye, and in one control person. However, lipstick is composed of such small amounts of these dyes that they hardly can cause toxic dermatitis provided that an exceptionally strong primary irritant is not used. In one of my cases (Case 2)

0.1 %. "Gelb fettlöslich" (Schimmel & Co.) produced a positive reaction to the skin on the thigh after the cheilitis had completely healed, even though the patient's lipstick did not contain the said dye². However I do not consider the reaction toxic, but it seems more likely that either this mixture of dyes contained TATAN or a substance chemically related to it, or then the patient had previously used lipstick which was composed of the said dye thus having become sensitized, even though signs of dermatitis had not yet appeared.

Lipstick dermatitis occurs comparatively seldom also on an allergic basis. *Sulzberger* & al. write: "In view of the almost universal use of lipsticks by modern women, the comparative rarity of cheilitis demonstrates clearly that the dyes used must be infrequent sensitizers, capable of producing clinical sensitivity only in exceptionally predisposed persons". Often sensitization is weak and restricted to the lips, and the healthy skin shows no reactions to patch tests. However, the literature on the subject also gives contrary cases in which strong reactions were elicited. One case of this type is the following:

Case. 1. A typographer, female, aged 32, had for approximately 15 years used various kinds of lipstick without any injurious effects. In September 1947 she brought a new lipstick, and after applying it for five times her lips began to swell on November 12, 1947. Before finding that cheilitis was due to the lipstick she still used it three times. The inflammation was always more severe on the day following use. In the beginning the edema disappeared within 2-3 days, but after the last application on November 22, 1947 the symptoms remained rather severe for about two weeks. At that time one could observe erythema, edema, vesicles and oozing on the lips and the surrounding skin. The tip of the tongue was also severely inflamed. Between attacks she could use some other kind of lipstick without any injurious effects.

On January 16, 1948 when cheilitis had almost completely healed patch tests were made with all the ingredients of the lipstick. TATAN alone caused a reaction. The violence of the hypersensitivity is distinctly revealed by the following: The patch tests were performed on the left thigh in three rows

² I made the patch test with this dye also in this patient (as a control case), when a new case of cheilitis due to lipstick containing it had come under my care. This case is not included in the material.

with TATAN in the middle. When the tests were removed after one day, the test materials were wiped off in the order of the rows with the same cloth. Thus, TATAN spread over the area covered by the second and third adhesive tapes. On the following day erythema and edema had developed over this entire area and the original reaction had become stronger. Healing took over a month.

According to the literature on the subject it seems that the patch tests are generally performed with the pure dyes as such. The above case in which the hypersensitivity was exceptionally strong shows, however, that there is not always reason to use them in such a strong concentration. The amount of the dye, which on removing the tests, spread to an area of ca. 250 cm^2 was exceedingly small per cm^2 . It was, however, sufficient to cause an edematous reaction over the entire area.

Strong reactions of this type which trouble patients intensely may, however, be avoided at least to a certain extent by performing a preliminary test with the lipstick itself. This usually contains only 1 % of the dye which in this concentration in general brings about a markedly weaker reaction than used as such. In so far as this reaction is weak or negative, the patch tests can be performed with the pure dyes without there being reason to fear very strong reactions. In a contrary case the patch tests must be performed with very weak concentrations. One must, however, always inform the patient that on the commencement of severe itching the test may be removed and the skin carefully cleansed.

In another case too TATAN gave an exceedingly strong reaction (severe edema, vesicles, which in the center ran together to form a bulla) (Fig. 2). In the third case the reaction was distinctly weaker. In the former (Case 2) a patch test was also performed with 1 % TATAN obtained from another factory. The reaction thus elicited proved that a hypersensitivity to the dye itself was present and not to impurities. 1 % xylene-azo- β -naphthol ($\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$ = Sudan II) and 1 % benzene-azo-benzene-azo- β -naphthol ($\text{C}_{22}\text{H}_{16}\text{N}_4\text{O}$ = Sudan III) gave definitely positive reactions (no reaction

was elicited in ten control persons)³. Thus hypersensitivity had also developed towards other, chemically related dyes. Because of the painful effect in the patient of several positive reactions possibly elicited it is, however, difficult to investigate

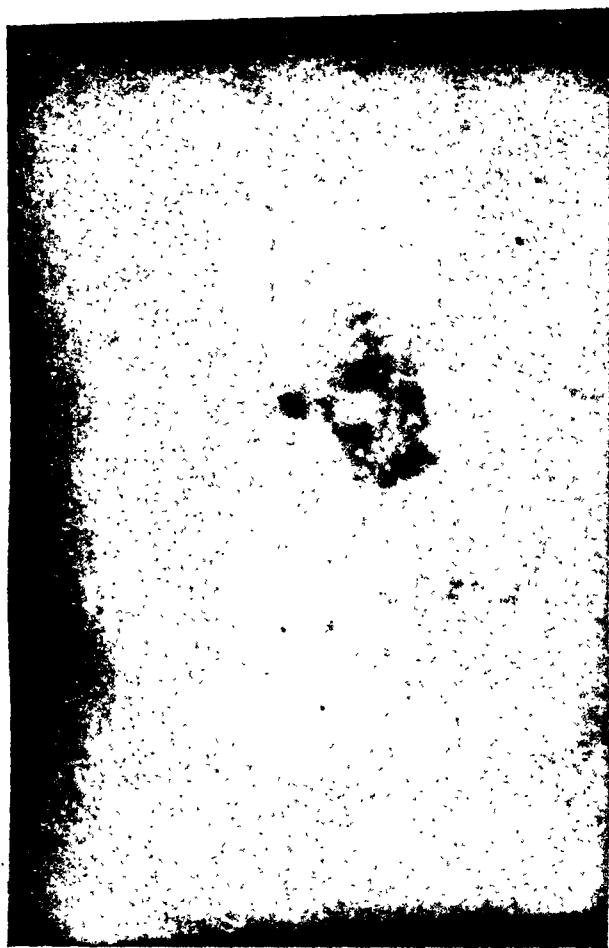


Fig. 2.

to how distantly related substances the hypersensitivity exists. In this case a patch test was made in addition with 10 % β -naphthol, with a negative result. In some cases *Sulzberger* & al. also obtained positive reactions with more than one

³ At least Sudan III has been reported to cause dermatitis. *Schwartz, Tulipan & Peck* recommend a 5 % concentration for the patch test.

azo-dye. These observations disclose that as regards sensitized persons it is not sufficient on selecting a new lipstick that the dye which caused the dermatitis is replaced by any dye whatsoever. Before using a new lipstick it is absolutely necessary to perform a patch test with it to prove that it does not contain such dyes related to the original one towards which hypersensitivity is already present.

Period of Sensitization. In the cases in which the patch test showed a strong hypersensitivity the period of sensitization was short. In Case 2 cheilitis appeared already five days after the patient had applied the lipstick for the first time (it is, however, possible that some other lipstick used sometimes previously had caused the sensitization), and she used it still three times before the cause of the dermatitis was discovered. In Case 1 the patient had used the lipstick five times within approximately two months before the onset of the cheilitis. She also used the lipstick still three times, which further increased hypersensitivity. In the third case, in which hypersensitivity was distinctly milder, the period of sensitization was considerably longer. For approximately two years the patient had used the same type of lipstick. Also in the case in which a weak hypersensitivity to the "Mitzi" lipstick was established, the dermatitis did not appear until the patient had used it about 40 times. It is evident that in the former two cases the patients were exceptionally predisposed to sensitization. For this reason their dermatitis began rapidly and hypersensitivity was strong.

Localization. In all the four cases the skin around the lips was also affected. In one patient, who used the lipstick also as rouge, dermatitis also appeared on the cheeks. There the signs were distinctly more severe than on the lips. This was perhaps due to the stronger predisposition of the skin to sensitization. Thus according to *Sulzberger & al.* sensitivity of the mucous membranes to contact substances occurs extremely rarely. However, several cases have been reported (*Sainz de Aja, Putkonen* etc.). In one of my cases the tongue was simultaneously inflamed.

Conclusions. It seems that in the manufacture of lipstick toluene-azo-toluene-azo- β -naphthol (TATAN) as compared to other dyes used in Finland at present relatively often causes sensitization. In addition, even a strong hypersensitivity towards TATAN may develop rapidly. Owing to these facts TATAN may be considered a too strongly sensitizing substance as regards the requirements placed on dyes to be used for this purpose. Therefore the said factory has, on my proposal, replaced TATAN by other dyes. New lipstick, which does not contain TATAN, but which is of the same shade as their previous lipstick, was made for all the patients. They have since remained well (an observation period of 8-12 months). Neither have there been any reports that the product on sale now has caused sensitization.

SUMMARY

The author has in three cases of lipstick dermatitis demonstrated hypersensitivity to an azo-dye (toluene-azo-toluene-azo- β -naphthol = Sudan IV = TATAN). The factory which manufactured the said lipstick received complaints of three additional cases. The lipstick used in these cases too contained TATAN, but the patients could not be examined. In addition the author established one case in which the product of another factory had caused cheilitis. Hypersensitivity was in addition demonstrated to xylene-azo- β -naphthol (1 %) and benzene-azo-benzene-azo- β -naphthol (1 %) in one of the cases in which the patch tests were performed with these related substances which the lipstick did not contain. In two cases the hypersensitivity was exceptionally strong and the author discusses possibilities to avoid too severe reactions on performing patch tests. In one of these cases cheilitis appeared already when the lipstick had been applied for only 5 days. In all the cases the skin around the lips was also inflamed. In one case in which the patient used the lipstick as rouge dermatitis also appeared on the cheeks. In one case the tip of the tongue was strongly inflamed. On the proposal of the

author the factory replaced TATAN with other dyes and furnished the patients with lipsticks not containing TATAN. Thereafter no recurrences took place (period of control 8-12 months).

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INVESTIGATIONS OF THE FUNCTION OF THE SUPRARENAL CORTEX IN ALLERGIC DISEASES¹

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Preliminary Report.

INTRODUCTION

In his *Theory of the General Adaptation*, Selye, the Canadian scientist, emphasizes the great importance of the adrenal cortex. We shall here give a short summary of this theory because it is closely related to our investigations.

If the body, for a certain time, is under relatively hard strain, such as strenuous physical exercise, high or low temperatures, infections, poisonings, clinical or physical shock, it reacts with a series of symptoms, the purpose of which is to increase the resistance of the organism. This reaction is chiefly due to cortical activity.

First appears an *alarm reaction*, of which the first part, the so-called *shock stage*, is passive with symptoms of hypothermia, hypotonia, hemoconcentration, increased capillary permeability, hypochloremia and nervous depression. Then a *contra-shock* follows, the defence reaction of the body; this is supposed to be brought into action through the activity of the adrenocorticotrophic hormone, which is secreted by the anterior pituitary gland. This gives rise to an increased

¹ Read Sep. 30, 1949, at the Second Northern Congress of Allergy in Helsinki.

secretion from the adrenal cortex, resulting in hyperchloremia, decreased capillary permeability and a shortened bleeding time. In addition to this, the liberation of histamine from the cells decreases while the antitryptic activity of the serum increases.

After this the body remains in a *stage of resistance*, with increased resistance against the causing irritant but with decreased resistance against other irritants. If, for a sufficiently long period, the body is exposed to stress of a different kind, against which it is unable to build up resistance—either because of the strength of the irritant or because of insufficient ability to adapt itself—it falls into a *stage of exhaustion*. The symptoms of this and the so-called *diseases of adaptation*, which appear in connexion with it, are due to the individual inability in adaptation. The excitant can give rise to either an increased or a decreased cortical excretion and to various ensuing disorders. Some types of hypertension, arteriosclerosis and nephrosclerosis are supposed to belong to the diseases of adaptation and to be caused by *increased* action of the adrenal cortex. Addison's disease and the closely-allied hypo-adrenia are supposed to be caused by *decreased* action of the adrenal cortex.

If Selye's general adaptation syndrome is a normal occurrence, in what relation to this do the allergic diseases stand? Do allergic patients react in an individual way or could it be that, in regard to adaptation, *all the different allergic diseases form a common group with a common cause: an endocrine disturbance due to insufficient adaptation?* The hypo-adrenia is probably best suited for the explanation of such a theory. The hypo-adrenic diseases are supposed to result from insufficiency of the cortex, which in turn is due to either a constitutional inferiority or to some superior stress.

The clinical symptoms of cortical insufficiency are loss of weight, fatigue, adynamia, hypotonia, pigmentations of skin and mucous membranes, and gastrointestinal and menstrual disturbances. The symptoms are very variable. They are

usually mild in cases of relative insufficiency and grow in intensity if the insufficiency develops into Addison's disease proper.

Many of the symptoms mentioned above are present in allergic diseases, but it must be borne in mind that loss of weight, fatigue and adynamia are common in many chronic diseases. Hypotonia is so common in allergy that there is reason to doubt the presence of allergy in cases where hypotonia is absent. Or one has to look for other, possibly transient, diseases that raise the blood pressure. *Duke's* opinion is that allergy is the most common cause of hypotonia. Predisposition to vertigo, vasomotor lability, cold and moist skin, which are described as symptoms of hypo-adrenia, are common also in allergics. Diarrhea and variable hypo- and hyperacidity-symptoms, which are incurable by drugs and dietetic treatment and which, as pointed out by *Maranon*, may be due to hypo-adrenia, are also frequent in allergic diseases. The same is true of different kinds of menstrual disturbances.

Hyperpigmentations are less common in hypo-adrenia than in Addison's disease proper. Many allergic patients present slight brown pigmentations especially on the arms and hands, dark-coloured skin around the eyes, as well as freckles, and they easily become sunburnt in summertime. All this resembles very much the descriptions of persons suffering from hypo-adrenia.

It is also of interest to notice how similar allergic anamnestics are to those described as typical of hypo-adrenia. We only wish to mention the occurrence of the symptoms in connexion with heavy physical strain, exposure to heat, cold and very bright sunshine, and, in particular, those observed afterinfections.

It is difficult to evaluate these symptoms, which occur in many diseases, because of the person factor in their interpretation. They indicate, however, that there are some similarities between hypo-adrenia and allergy which justify a closer investigation of the three groups of hormones upon which the action of the adrenal cortex depends.

These three groups are:

Desoxycorticosterones (salt-water factor),
 Glucocorticosteroids (sugar factor),
 17-ketosteroids (protein factor).

WATER-SALT METABOLISM

The salt-water hormone (*desoxycorticosterone*) has its main influence upon the metabolism of potassium, sodium and chlorides in the body. Normally, a sufficient amount of sodium chloride is resorbed back from the glomerular filtrate, and only the superfluous amount is rapidly excreted by the kidneys. In this way, normal electrolyte equilibrium and osmotic pressure are maintained in the body. In DOCA-insufficiency the kidneys lose their ability to accomodate themselves rapidly to varying salt and water intakes. The capillary permeability and the diffusion of chlorides to the interstitial spaces increases. The result is hypochloremia and a decrease in blood sodium values. The potassium content of the blood increases simultaneously, probably through mobilisation of intracellular potassium. Due to the disturbed electrolyte metabolism, there is increased water excretion through the kidneys and the intestine.

Low sodium and chloride values of the blood and simultaneous high potassium value are classic symptoms in cortical insufficiency. But these symptoms are not always present even in severe Addison's disease. Often the tolerance tests are the only means of demonstrating disturbances in the water-salt metabolism. The test presented in 1941 by *Robinson, Power and Kepler* is the one most used in examination of the salt-water factor, for which reason we have chosen it in our investigations.

Kepler test: The day before the test, the patient is allowed to eat normal food, without any additional salt or DOCA intake. After 6 p.m. the patient must not eat or drink. The urine is collected between 10.30 p.m. and 7.30 the following morning. The amount is measured and a sample is kept for examination. The bladder is emptied at 8.30 a.m. Between 8.30 and 8.45 the patient

has to drink 20 ml. water per Kg. body weight. The bladder is emptied at 9.30, 10.30, 11.30 a.m. and 12.30 p.m. Every portion is measured. If the amount of the night's urine is larger than any of the hourly day-portions, the result of the first part of the test is positive. For the second part, the chloride and urea values for serum and nighturine are determined and the result is calculated by the following formula:

$$\text{Index} = \frac{\text{urine urea in mg \%}}{\text{serum urea in mg \%}} \times \frac{\text{serum chlorides in mg \%}}{\text{urine chlorides in mg \%}} \times \frac{\text{largest day urine portion in cc}}{\text{night urine in cc}}$$

If the index is less than 25, the test speaks in favour of a present cortical insufficiency (a condition being, however, that the patient does not suffer from any organic disease of the kidneys). If the index is higher than 30, insufficiency is very unlikely but still possible.

We have performed the Kepler test on 64 allergic patients, of whom 46 suffered from asthma and the rest from eczema, urticaria, migraine and allergic rhinitis (Table 1). As controls 10 healthy subjects were used; these all had a completely negative Kepler test.

Part I was positive in 23 cases (35 per cent), of which 20 suffered from asthma.

Part II was positive in only 7 cases (10.9 per cent) of whom 4 had asthma, 1 chronic eczema and 2 asthma and eczema. All the patients in whom both parts of the test were positive had suffered from their severe disease for many years (4-21).

It was not possible to find any special characteristics for the Kepler-positive patients, either in regard to etiology (pure allergies, infections) or to blood findings etc. compared with the other investigated allergies. In the group of completely Kepler-negative cases, there were patients whose diseases were of the same duration and severity as in the first group.

The serum sodium, potassium and chloride values were determined in 23 patients, of whom 18 suffered from asthma

Table 1.
Important symptoms and laboratory findings in seven Kepler-positive cases of allergy.

Patient	Sex	Age	Disease	Duration of symptoms years	SR	Blood pressure mm Hg	Kepler's test index	Sodium in serum mg%	Potassium in serum mg%	Chlorides in serum mg%	Lymphoc. %	Eosinoph. %	Dextrose tolerance test mg%
1	M	5	A + E	5(E) 3(A)	5—19	105/75—125/95	18.6	307	18.8	351	43	13	104—208—179
2	F	8	E	6 1/2	6—54	100/65—105/75	18.7	316	20.2	360	48	20.5	87—102—114 85—103—117 106—158—126
3	M	55	A + E	7	27—42	110/90—135/95	15.2	347	20.6	372	29.5	10.5	118—185—181
4	M	22	A	21	4—9	105/70—115/75	6.8	320	21.5	343	43	10	102—185—162 96—162—157
5	M	13	A	4	4—7	100/60—115/75	26.7	315	16.0	358	49	6.5	108—156—138
6	F	37	A	11	12—22	95/——125/100	12.4	360	15.5	349	32	10	92—161—138
7	F	62	A Polyarthrit. chr. Hyperthyrosis	12	14—57	120/80—135/80	12.9	—	—	360	45	14.5	107—195—187

and the rest from eczema, urticaria and allergic rhinitis. The potassium value was extremely high (28.5 mg% ; normal 18-23 mg%) in one and slightly elevated in 9 cases. All patients with high values suffered from asthma. Seven cases had low-normal or slightly sub-normal sodium and chloride values. (Normal values for sodium 320-350 mg%, for chlorides 330-370 mg%). Three patients, all suffering from asthma, had simultaneously low sodium and high potassium values. These three were all severe cases. They had suffered from their disease for 5, 6½ and 21 years respectively.

An attempt was made to use the potassium tolerance test described by *Cutler, Power and Wilder*, in which the patient during at least three days gets a diet high in potassium and low in sodium chloride content. The patients, however, were not able to take the diet because of nausea and vomiting.

METABOLISM OF CARBOHYDRATES

The group of *glucocorticosteroids* (sugar hormones) plays an important rôle in the regulation of the metabolism of carbohydrates, partly in connexion with other cortical hormones. An insufficient excretion of the salt-water hormone disturbs the phosphorylation process of the sugar, which is necessary for the normal resorption of sugar from the intestine to the blood and from the blood to the tissues. Insufficiency of the sugar hormone excretion disturbs the normal glyconeogenesis, i.e. the formation of glycogen from proteins and in some degree from fat. As a result of this the blood sugar value is low, the liver and even other tissues become poor in glycogen and the muscular energy diminishes. Hypoglycemic symptoms appear at higher blood sugar value than in normals, and the insulin tolerance decreases. The defence mechanisms of the body are weakened. This manifests itself especially in sensitivity to strain, lack of oxygen, differences in temperatures, and in an increasing sensitivity to infections. Both desoxycorticosterone and glucocorticosteroids raise the minimal lethal dose of histamine even in normal animals.

It has been shown that in adrenalectomized animals the histaminase content of the lungs is smaller and the histamine content of the intestine and of the blood three times higher than in normal control animals.

This facilitates, according to *Wilson*, the appearance of shock.

Dougherty & White moreover have shown that the amount of eosinophil cells and lymphocytes in the blood increases with insufficiency of the sugar factor.

In order to get an idea of the resorption and the further metabolism of the carbohydrates in allergic disturbances, we have used the following tests:

1. *Double dextrose tolerance test per os* (Staub).
2. *Insulin tolerance test.*
3. *Adrenalin tolerance test.*

An investigation of the number of lymphocytes and eosinophil cells in the blood of allergics was also made in order to assess their possible relation to allergy.

Double dextrose tolerance test.

The double dextrose tolerance test is performed in the following way:

The patient drinks 20 per cent dextrose water—an amount corresponding to $1\frac{1}{2}$ Gm. dextrose per Kg. body weight—on empty stomach, and the same dose $1\frac{1}{2}$ hours later. The blood sugar value is determined every 30 min. during 3 hours, by the Hagedorn-Jensen method.

A so-called "*Staub effect*" appears normally in this test; i.e. the second dose gives a smaller rise in the blood sugar value than the first. The reason for this is not entirely known, but it is supposed that all the counteracting mechanisms attempt to normalize the blood sugar value. In cortical insufficiency this effect is absent in more than 50 per cent of the cases. It is likewise normally absent in children below 2 years of age. This is probably due to the fact that the cortical

activity is not yet wholly developed at that age. Absence of the Staub effect can be considered abnormal only after puberty.

We performed 45 double dextrose tolerance tests on 35 patients. The Staub effect was absent or quite small in 17 cases. If, from these 17 cases we exclude the 7 patients who were under 5 years, and in whom the Staub effect even normally may be absent, there are 10 cases left. Eight out of these 10, who were older children and adults, had values near the normal. Only 2 cases showed a markedly higher rise in the blood sugar value after the second dose than after the first.

It is very difficult to judge this test, because many factors play a part in it. The motility of the stomach and the intestines influences the rapidity with which the sugar is transported to the place of resorption; the rapidity of the resorption itself has a clear effect on the formation of the blood sugar curve; and last, but not least, the whole counter-regulatory apparatus with its enzymes and hormones plays a very important rôle.

The only phenomenon which repeated itself regularly in these tests was that the blood sugar values rose rapidly and to values near the upper limit for the normal. It is likely that these patients had neither delayed nor decreased sugar resorption.

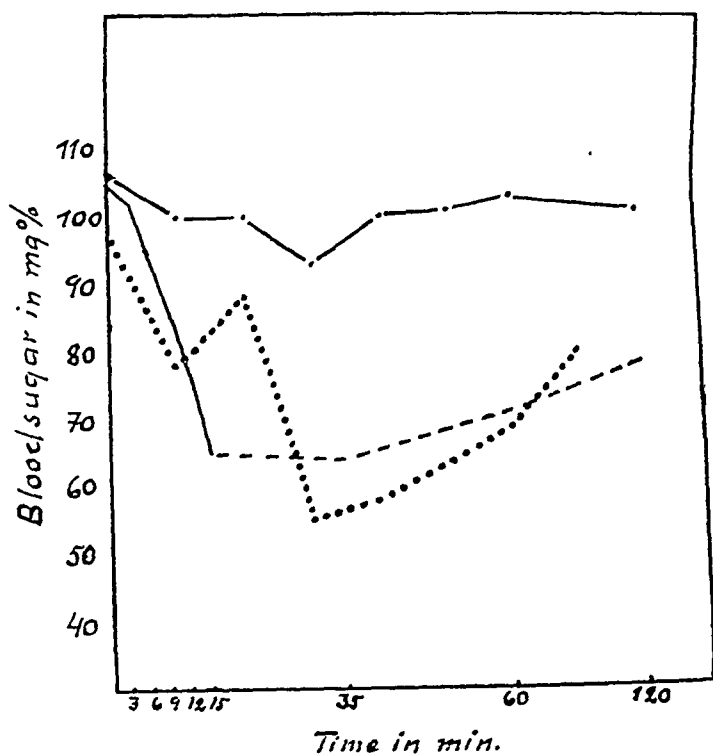
Insulin tolerance test.

An intravenous or intramuscular injection of insulin in a normal person, causes a small and transient rise in the blood sugar value. After a so-called *latency time*, the blood sugar value falls below the starting level. The length of the latency time is normally between 4 and 10 min. If the counteracting regulation is intact, a reactive adrenalin excretion follows, and the blood sugar value is again normalized in about half an hour. With a dose of 0.1 units per Kg. body weight the maximal limit for the blood sugar decrease is 30 mg%.

It is probably of importance in the evaluation of the insulin tolerance test to observe the latency time. The insulin meets blood and tissues in a normal state during the first minutes after the injection. Later, the body mobilizes all its counteracting forces and the reaction becomes very complicated and difficult to evaluate. A possible insufficiency of one component can be compensated by the hyperfunction of another.

We have not, in the literature so far published, been able to find information about the insulin latency time in cortical insufficiency. As already mentioned, the blood sugar value normally falls only slightly and is again normalized

Table 2.
Insulin tolerance tests.



— · — · — normal curve (Kappert).

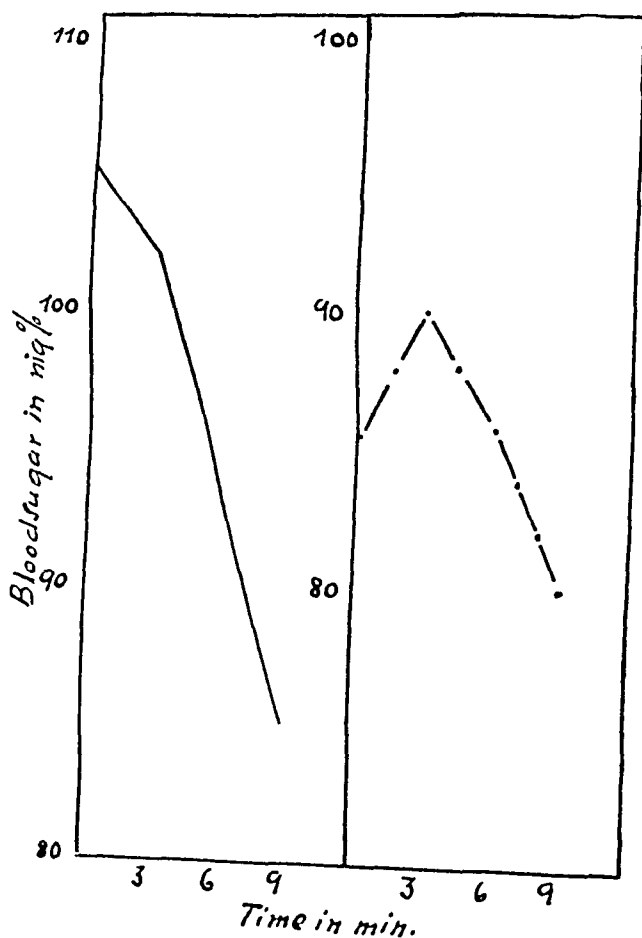
———— average curve of 20 allergic patients (----- referring only to 6 cases).

..... curve of patients with Addison's disease (Kappert).

in half an hour. The only symptom connected with this is a more or less pronounced feeling of hunger. If the counter-regulation is inadequate, as in case of cortical insufficiency, hypoglycemia appears in the course of an insulin tolerance test. The blood sugar falls continuously, remains low for $\frac{1}{2}$ -1 $\frac{1}{2}$ hours, then rises slowly to normal values. The patients with cortical insufficiency are more susceptible to insulin and have a more severe reaction to hypoglycemia.

The insulin tolerance test has been performed on 20 al-

Table 3.
Insulin Latency Time.



— average curve of 20 allergic cases.

- - - - - average curve of 15 normal children, aged 2-7 years.

lergic patients of whom 15 suffered from asthma, 3 from allergic eczema, one from migraine and one from allergic rhinitis. All got the prescribed dose of 0.1 unit per Kg. body weight, intravenously.

Fourteen of the patients reacted with such severe symptoms of hypoglycemia that we had to break off the test in order to prevent shock symptoms. In spite of oral administration of glucose 12 min. after the insulin injection, a boy aged 12 got a distinct shock with unconsciousness and convulsions.

The insulin latency time was, in 12 cases, under 3 min.; in 7, under 6 min.; and in one between 9 and 12 min. The average blood sugar decrease was 43 mg% in 12 min.

The time when the initial sugar level was reached could not be determined because of the necessity to discontinue most of the tests.

Adrenalin tolerance test.

In order to get an idea of the influence of adrenalin upon the blood sugar in allergic patients, 10 so-called adrenalin tolerance tests were performed. The dose of adrenalin administered was 0.014 mg. per Kg. body weight, given subcutaneously. The blood sugar values were determined after 10, 20, 40, 60 and 120 min.

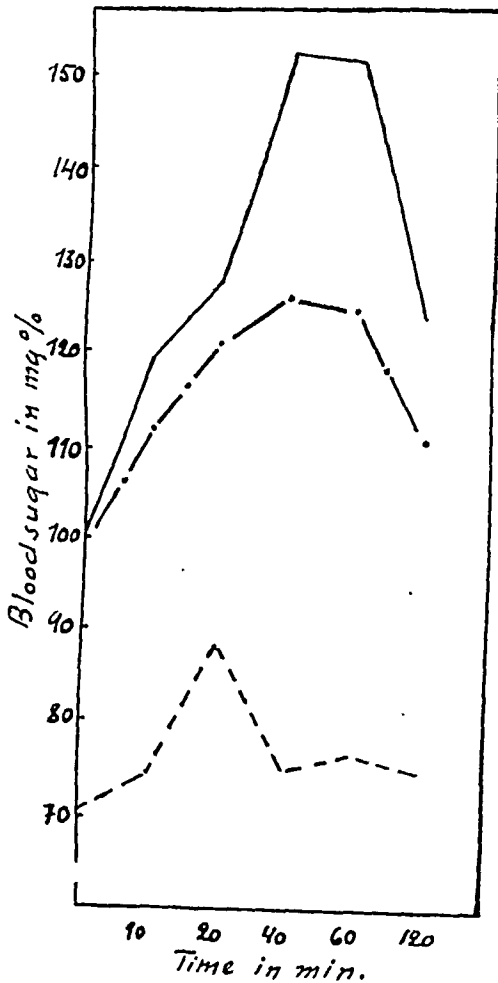
The adrenalin tolerance test is presumed to give a picture of the glycogen content of the patient's tissues. The adrenalin dose used, normally raises the blood sugar value by about 45-60 mg%. If the glycogen content of the liver is diminished, adrenalin is unable to mobilize it in comparative quantities, and the elevation becomes smaller. This happens in cortical insufficiency where the glyconeogenesis is disturbed and the glycogen reserve of the liver is reduced.

Of the patients tested, 8 suffered from asthma and 2 from allergic eczema. Only one case, a patient with eczema, reacted with an increase in blood sugar as high as 46 mg%, a value which still has to be considered low. Eight cases showed blood sugar increases of 13-40 mg%. The average rise being 25

mg%. One of the patients reacted with a decrease of the blood sugar value. To 4 of the patients, adrenalin had never been administered before; to a further 4, not during recent months.

The result thus cannot depend upon the possibility that frequent adrenalin injections might possibly have emptied the liver glycogen reserves of the patients.

Table 4.
Adrenalin Tolerance Tests.



- normal curve (Kappert).
- · - · - average curve of 10 allergic cases.
- - - - - curve of patient with Addison's disease (Kappert).

WHITE BLOOD CELL COUNT

From the white blood cell counts, performed on every patient at our hospital, we have observed that not only the eosinophiles but also the lymphocytes often show values higher than those found in normal persons. That high numbers of eosinophils are usually found in allergic diseases, is well-known. As to the lymphocytes, we have not in the literature been able to find an increase of them mentioned in connexion with allergic diseases.

In order to investigate this question, we have studied the material obtained at our hospital. In order to get a correct picture of the factors concerned, cases showing signs of infection have not been taken into consideration. So all cases with a sedimentation rate above 10 have been left out.

Our material thus obtained consists of 220 cases, divided as follows:

Bronchial asthma	131 cases:	76 children + 55 adults.
Eczema allergicum	73 " :	50 " + 23 "
Rhinitis vasomot.	16 " :	9 " + 7 "
<hr/>		
Total:	220 cases:	135 children + 85 adults.
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Table 5 shows eosinophiles thus obtained, compared to a normal curve by *Carstanjen*. This curve shows clearly the well-known fact that the eosinophiles are abnormally increased in allergic diseases.

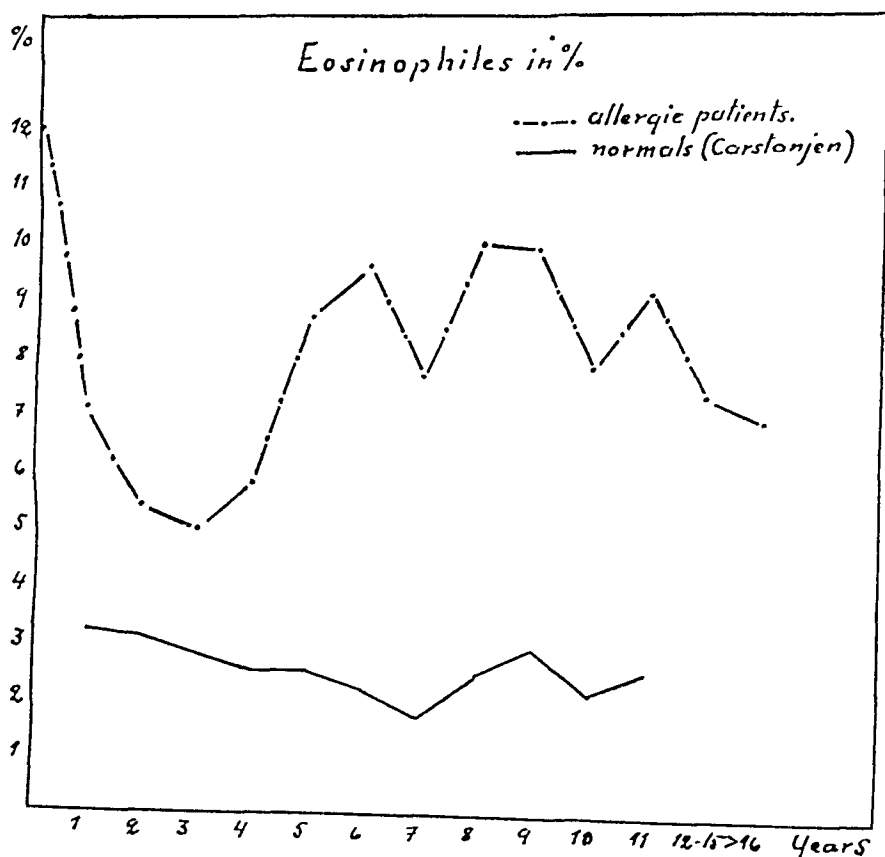
Table 6 shows the values of lymphocytes in our material, compared to lymphocyte counts in normal persons according to *Brock* and to *Carstanjen*.

Our material is small and needs to be enlarged. But it shows that, in allergic diseases, there seems to be an increase not only in eosinophiles but also in lymphocytes.

The combination eosinophilia and lymphocytosis is often in the literature mentioned in connection with disturbances in the function of the adrenal cortical hormones, whose function is regulated by the anterior pituitary gland.

Investigations by *Dougherty & White* show that extirpation of the adrenal cortex in rats causes atrophy of the lymphatic tissues. Insufficiency of the adrenal cortex, mainly of its glucocorticoid hormones, is also connected with increase in eosinophiles and lymphocytes. The same has been observed in Addison's disease, which is due to atrophy of the adrenal

Table 5.



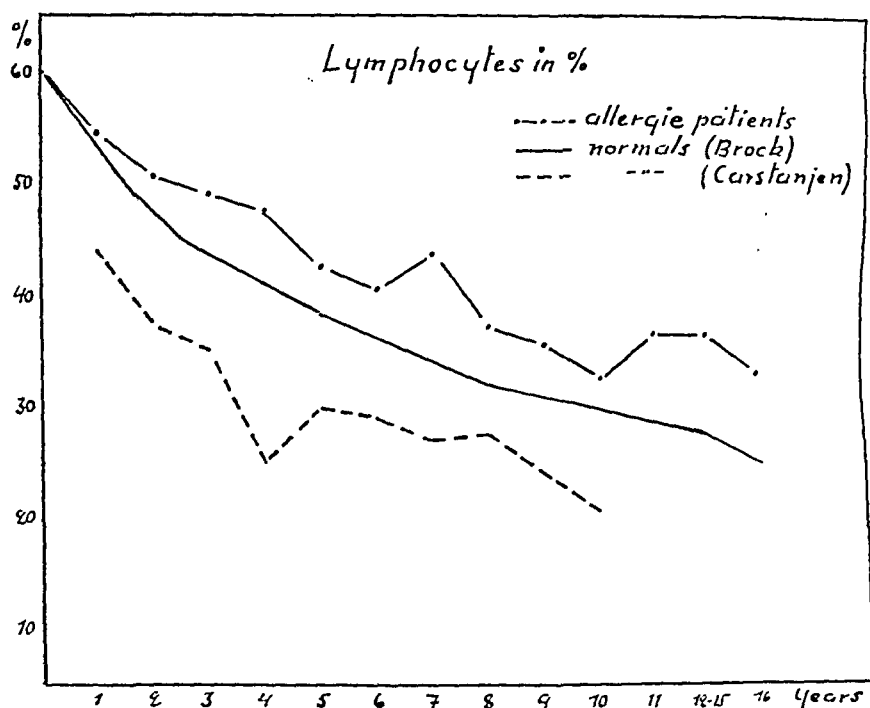
cortex. Insufficiency of the adrenal cortex may be the result of a chronic infection and also in such cases lead to lymphocytosis.

If, on the other hand, a normal animal is injected with sugar hormone from the adrenal cortex or with adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which stimulates the production of adrenal cortical

hormones, the result is a liberation of lymphocytes from the spleen and their dissolution in the blood, resulting in their decrease.

According to *Forsham, Thorn et al.*, the injection of 25 mg ACTH into a normal person with undisturbed adrenal cortical function, decreases the number of eosinophiles by at least 30 per cent, at the same time showing a remarkable decrease in lymphocytes also.

Table 6.

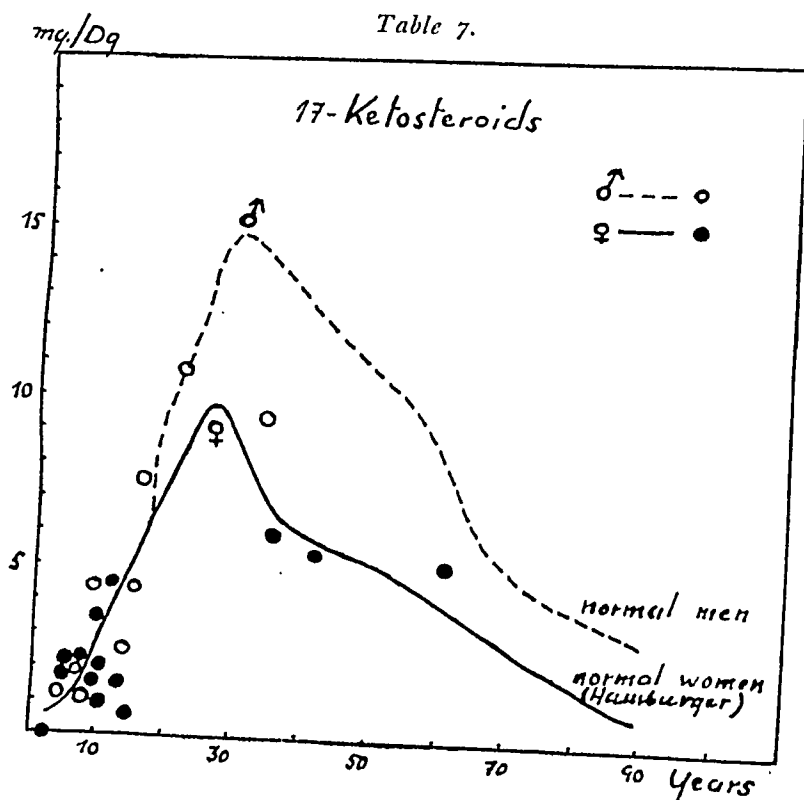


17-KETOSTEROIDS

In the urine are excreted a number of steroids with a ketone group bound to the C-atom 17. Even if these are not real cortical hormones, but are considered to represent the end products of androgen metabolism, the prevalent opinion is that in women they give a good picture of the excretion of

the protein factor from the adrenal cortex. In men they are considered to be the sum of excretion of the protein factor and of androgens.

The content of 17-ketosteroids in urine is usually determined by *Callow's* modification of *Zimmermann's* reaction, which is a spectrophotometric method with correction for unspecific substances. Different normal values have been determined, the differences being probably due to variations



in the sexual fertility of different communities living in different latitudes. In Scandinavia, *Hamburger* has determined the normal excretion of 17-ketosteroids in different age-groups. He examined 250 healthy Danish males and females aged between 2 and 102 years. The values he obtained are similar to those determined by *Engstrom & Mason* in America. They show maximum excretions between 20 and 40 years of age,

with an average daily output of 16 mg for males and 10 mg for females.

In cases of hyperactivity of the adrenal cortex, the output of 17-ketosteroids is increased; it is decreased in cases of insufficiency. In cases of pituitary basophilism (Cushing's disease) a daily output of up to 170 mg. has been shown. In a material of 6 cases of Addison's disease (5 men and 1 woman) *Luft & Sjögren* got values ranging from 4 to 11 mg. per day. The determination of the excretion of 17-ketosteroids cannot be greatly relied on, because too many factors have an influence on it. It is thus shown that gastrointestinal and liver disturbances, anemias, starvation, and shock suppress their excretion. We have tried, as far as possible, to eliminate such factors from our material. Infections also cause a decrease in 17-ketosteroid output. These we have not been able to eliminate completely, because of their intimate connexion with allergy.

In our material, the daily output of 17-ketosteroids was determined in 24 patients, aged between 3 and 62 years. Nine were males and 15 females. Nineteen suffered from asthma, 3 from eczema, and 2 from both asthma and eczema. The determinations were performed in the chemical laboratories of the University of Helsinki.

The following table (Table 7) shows the results, compared with normal values reached by *Hamburger*. The values obtained to a great extent follow the normal ones. Only in 6 cases can a considerable difference from the normal be ascertained. Five out of these 6 were children: one boy and 4 girls. The sixth was a man aged 37. He suffered from severe asthma and showed a value of 9.2 mg. In the urine of one of the girls mentioned above, no 17-ketosteroids at all could be determined. This girl was 3 years old and suffered from asthma. Another girl, aged 12, showed a value normal for a 7 year old child. She suffered from a very severe asthma which had persisted for many years and markedly weakened her general condition and delayed her physical development.

SUMMARY

In an investigation of the function of the suprarenal cortex hormones in patients suffering from allergic diseases, such as bronchial asthma, allergic eczemas, vasomotor rhinitis, etc., the following data was obtained:

1) *The water-salt metabolism.*

The first part of the *Robinson-Power-Kepler* test was positive in 23 out of 64 patients (35 per cent). In 7 (10.9 per cent) of these 64 patients a positive second part of the test also could be carried out, *pointing to a disturbance in the secretion of the desoxycorticosterons.*

Potassium, sodium and chlorides were determined in 23 cases. The potassium value was increased in 10 cases. Seven cases showed low values of sodium and chlorides. Only 3 cases (all asthmatics) showed both high potassium and low sodium and chloride values, as often are seen in Addison's disease.

2) *The carbohydrate metabolism.*

The *double glucose tolerance test (Staub)* was performed in 35 cases. Most of the patients showed a marked initial rise of the blood sugar, pointing to a good resorption of sugar from the intestines.

The second part of the curve was higher than the first in 17 cases of which 7 were children below 5 years of age, at which age it normally can be higher.

The *intravenous insulin tolerance test* was performed in 20 cases. In no case could the normal initial rise of blood sugar be seen. The blood sugar level decreased rapidly: latency time in 12 cases was less than 3 min.; in 7 cases 3-6 min.; and in only one case 9-12 min.

Following this fall in blood sugar, the patients showed an increased sensitivity to hypoglycemia. Fourteen cases had such severe symptoms of weakness, sweating and anxiety that the test had to be discontinued by the administration of glucose, in order to prevent shock symptoms. In spite of this,

one boy of 14 with severe asthma experienced a severe shock with unconsciousness and convulsions.

In 10 cases *the adrenalin tolerance test* was performed. The blood sugar, which in this test normally increases 45-60 mg%, showed in 8 of the cases an average increase of 25 mg% (13-40 mg%). In one case the blood sugar decreased. Only one case showed an increase, amounting 46 mg%, which still must be considered a low value.

3) *The white blood cell count.*

The *white blood count* performed in 220 allergics without signs of infection, showed an abnormal increase in both lymphocytes and eosinophiles.

4) *The 17-ketosteroids.*

The *determination of 17-ketosteroids* in the urine of 24 allergic patients by the Zimmermann-Callow method, gave abnormal low values in 6 cases, compared with *Hamburger's* normal curves.

These investigations of the function of the adrenal cortex hormones in allergic diseases show, by the methods used, a disturbance in the water-salt metabolism and a decrease in the secretion of 17-ketosteroids only in a small percentage of the cases. From the results obtained by the insulin and adrenalin tolerance tests carried out, it might be concluded that in allergic diseases there is a disturbance in the carbohydrate metabolism, which seems to be due to a relative insufficiency of the Sugar Hormone of the adrenal cortex. In the same direction point the lymphocytosis and eosinophilia, observed in the white blood count of the allergics.

In the light of this, the authors assume the allergic diseases to be a group of Diseases of Adaptation (Selye), due to a relative Insufficiency of the Adrenal Cortex.

DISCUSSION

Opinions differ with regard to the interrelationship between the adrenal cortical hormones. However, disturbances in the salt-water metabolism are generally regarded as the most important symptoms of cortical insufficiency. In accordance with this, in allergic diseases one might also expect to find the essential disturbances in the water-salt metabolism. Recent investigations, however, indicate that cortical insufficiency can manifest itself mainly or even entirely through disturbances in the carbohydrate metabolism. (*Goldzieher, Hench, Kendall et al.*). *The present investigations show that in allergic diseases, disturbances in the water-salt metabolism only could be determined in a small percentage of cases, whereas disturbances in the carbohydrate metabolism were much more frequent and severe.*

The double glucose tolerance test (*Staub's*) showed in most of our cases that the resorption of sugar was good. This result confirms nicely our determined mostly normal function of the water-salt hormone, by which the sugar resorption is regulated. The Staub effect was normal or subnormal in most of the cases. It is not quite clear which are the regulators of this effect, but all forces are assumed to work together in order to normalize the blood sugar value. The Staub effect is absent in more than half of the cases of insufficiency of the adrenal cortex. It is also almost regularly absent in infants below two years of age, and often absent in bigger children.

The intravenous insulin tolerance test gave widely abnormal results. The time of latency was in most cases extraordinarily short. *Himsworth* discusses two main theories as explanations of the time of latency. According to the first, the insulin, at time of injection, is inactive, and the latency time is deemed necessary for its activation. No activating substances have, however, been demonstrated. According to the second theory, the blood contains anti-insulinary substances, which delay the action of the insulin during the latency time. Such anti-insulinary substances have been found in the

anterior pituitary gland, a less effective one in the thyroid, and a third is the glucocortical hormone of the adrenal cortex.

As in our material no cases have shown symptoms pointing to a disturbance of the pituitary-anterior or the thyroid, we assume that the shortened latency time demonstrated originates from insufficiency of the *sugar hormone excretion*. Investigations of the time of latency in Addison's disease mentioned in the literature we were not able to find.

Remarkable in our cases was also the decreased tolerance to hypoglycemia, which was seen in most patients. The generally accepted explanation of this occurrence is a decreased output of corticosteroid hormones. The possibility of a decreased excretion of adrenalin being the cause of this is ruled out by the fact that adrenalin is not excreted until the blood sugar level has decreased to about 70 mg% (Cameron).

The adrenalin tolerance test was performed in order to gain an idea of the influence of adrenalin upon the blood sugar in allergic patients. Adrenalin has for a long time been used in the treatment of allergic diseases and shock symptoms, particularly because of its power to raise the blood pressure. Its effect upon metabolism has been studied extensively (*Cori & Cori*). Adrenalin accelerates the rate of the enzymatic breaking down of glycogen in the liver and muscles, the ultimate products being, in the former, dextrose, in the latter, lactic acid. Following the injection of adrenalin, the glycogen in the liver decreases, the glycogen in the muscles remaining low. There is a reduction in the adrenalin effect if the enzymatic system of the liver is disturbed or its glycogen reserve depleted and also in case of hyperinsulinism. The adrenalin effect is decreased in insufficiency of the glucocorticosteroids, due to a disturbance of the glycogeneogenesis. The lessened ability of adrenalin to raise the blood sugar level in the cases observed by us, points to a decrease in the storage of glycogen in the liver, probably due to disturbed glycogeneogenesis. The increased sensitivity to hypoglycaemia, seen in the insulin tolerance test, points in the same direction.

The blood counts, performed in 220 cases of bronchial asthma, allergic eczema and vasomotor rhinitis, show that in these diseases there is not only an increase in the eosinophiles, as is well-known from the literature; the amount of lymphocytes is also abnormally increased.

This confirms nicely the investigations of *Dougherty & White*, showing that insufficiency of the adrenal cortex, mainly of its glucocorticoid hormones, is connected with an increase in eosinophiles and lymphocytes, confirming our theory that in allergic diseases there is an insufficiency of the adrenal cortex, mainly in respect of the glucocorticosteroids.

The determination of 17-ketosteroids in 24 allergic patients showed low values in 6 cases, compared to the normals. As it is not quite known what factors influence the excretion of the 17-ketosteroids, we do not wish to discuss their appearance at this early state of our investigation, as we suppose that there is a difference in their excretion, depending on the state of allergy of the patient in question.

Our investigations of the function of the adrenal cortical hormones in allergic diseases originated from the question of the *relation of these diseases to Selye's General Adaptation Syndrome*.

It seems too early to take a stand on this complicated question, as in this preliminary report we still lack investigations of the function of the adrenal cortex in the different states of allergy and in its different manifestations. However, we would like briefly to mention this interesting question.

When the organism is exposed to stress, it fights the shock with a defence reaction, the contra-shock. *Selye* explains this as the action of the adrenal cortical hormones, secreted through stimulation by the pituitary adrenocorticotrophic hormone. If the function of the adrenal cortex is sufficient, the state of resistance restores the body to normal. In allergic diseases in which a hereditary weakness in the adrenal function can be assumed, (according to the hereditary disposition to allergic diseases), or in which the weakness has been acquired

through lack of resistance to stress, the body *acquires no power of resistance, but enters the state of exhaustion*. This, in allergy, seems to be the *state between the attacks*, during which the patient suffers from symptoms of relative insufficiency of the adrenal cortical hormones, with decreased blood sugar values, increased sensitivity to hypoglycemia and increased influence of histamine. In this state everything that counteracts these symptoms, whether it be in order to restore or increase the function of the adrenal cortex (as do ACTH and other hormones, vitamins, sulphuradministration and increased wellbeing) or in order to remove the factors which have brought forth the stress (microorganisms and others), will help the organism to overcome the state of exhaustion and bring it back to health. This is the state in allergy where help is of greatest importance. If not successful, the organism has to go through the next state of shock and contra-shock, due to all the different kinds of stress that it reacts to.

On the other hand, in the *state of contra-shock*, i.e. the *state of allergic attacks*, the glucocorticosteroids themselves or the ACTH and other hormones, which increase their excretion, will be the substances chosen to help the organism out of this inconvenient and often dangerous state of contra-shock.

In this way the evidence of the insufficiency of the adrenal cortical hormones in allergic diseases will deepen our understanding of this complicated group of diseases and bring about a more successful treatment.

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EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS AND DISSEMINATED SCLEROSIS

A REVIEW

By

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Modern experimental studies of sclerosis are bound up with allergy. The term "allergy" must here be used in its widest sense. Clinical studies of disseminated sclerosis have shown that the pathogenesis of this disease can hardly be grouped with atopy, i.e. that type of allergy which is represented by asthma, hay fever and atopic dermatitis. The incidence of atopy does not seem any greater among disseminated sclerosis cases than amongst normal people (*Baer & Sulzberger, 1939*). However, when antigen-antibody reactions were produced experimentally in animals, the resulting clinical and pathologic pictures more or less resembled those of disseminated sclerosis in man. The relation of disseminated encephalomyelitis to disseminated sclerosis will not be further discussed here.

Historical Survey.

The first attempt to classify disseminated sclerosis as an allergic manifestation was made at the end of the 1920's. At that time, a number of cases of disseminated encephalomyelitis cropped up all over the world as the direct consequence of various infectious diseases, particularly after vaccinations and measles. Similar cases were also observed after Pasteur vac-

inations for rabies. There does not appear to be any exact information about the number of cases of rabies vaccination encephalomyelitis, but they were sufficient to open our eyes to the possibility that some of the neurologic complications of vaccination might be attributed to some kind of antigen-antibody reaction in the central nervous system. *Glanzmann* (1927) was the first to proclaim the possibility of an allergic pathogenesis in post-infectious encephalomyelitis, on both clinical and pathologic grounds. *Wohlwill* (1928) also came to the same conclusion from purely pathologic studies.

The basis of all modern allergic opinion was the experimental anaphylactic investigations published by *Rivers and his colleagues* in 1933, 1934 and 1935.

These investigations were based partly on earlier observations that rabbits sometimes became paralysed after injection of brain substance and partly on *Brandt, Guth & Muller's* (1925) confirmation that brain tissue contains an alcohol-soluble lipoid which can behave as a hapten, and which can therefore combine with heterologous protein.

Rivers, Sprunt & Berry (1933) therefore injected brain substance from rabbits as 50 injections intramuscularly into eight monkeys. Clinical signs of nervous disorder developed in two of them. Pathologic studies of the central nervous system showed scattered demyelinations and perivascular infiltrations, containing giant cells and eosinophils.

The following year, they injected intramuscularly into rabbits fresh homologous brain tissue supplemented with pig serum, or fresh homologous brain which had been exposed to vaccine virus, or autolysed homologous brain. In all cases, antibodies to brain were found in the rabbits' blood; they were more organ than species specific. Homologous brain substance alone did not give rise to antibody formation. The antigen in the white matter was 6 times that in the grey matter. Similarly, there was a relation between the amount of antigen and the development of myelin. Clinically, some animals were unaffected, others were paralysed in their hind-quarters; many died within a month in a state of severe

emaciation. The pathologic findings were difficult to assess. *Rivers & Schwentker* themselves were very much inclined to regard the condition as spontaneous encephalitis; a constant relation could be found between the antigenicity of the injected material and the number of paralysed animals.

The following year (1935), they injected rhesus monkeys with heterologous brain tissue (from rabbits), either in watery solution or as alcoholic extracts. After numerous intramuscular injections, they succeeded in producing neurologic signs in the monkeys. They found a histologic picture of disseminated encephalomyelitis in all these six, and also in one which had not shown any neurologic signs. Other monkeys and rabbits were injected with brain emulsions from the brains of the experimental animals. All remained healthy. No antibodies were found in the blood of the injected monkeys. The authors were inclined to believe that an unknown latent agent was activated by the injection.

These fundamental investigations are discussed thoroughly here, since they show the opportunities which the technique offers of studying encephalomyelitis, and also the indefinite and complicated problems which must be solved in order to gain a better understanding of these conditions.

The advantages of this technique are immediately apparent: a condition which in many respects resembles the human disease has, for the first time, been produced in animals.

The problems involved may be stated here: firstly, the pareses produced in the rabbits could not be satisfactorily explained by the pathologic findings. *Hurst* (1932) had the same experience with paralytic rabbits after injection of brain extracts into rabbits. In our material also (*Fog & Hertz*, 1949) no agreement could be found between the clinical picture and the pathologic findings, and therefore no satisfactory explanation of the rabbits' disease could be given. A number of rabbits showed no histologic changes in their nervous system, central or peripheral, in spite of widespread paralysis. On the other hand, an antibody to the brain could

be demonstrated in the rabbits, though not in the monkeys, which, however, showed a definite correlation between their clinical and pathologic pictures.

The problems requiring solution can therefore be summed up in the following questions:

(i) Is the reaction produced in the experimental animals an allergic reaction depending on an antigen-antibody reaction?

(ii) Can this reaction by itself cause disease, and is its morphologic basis a disseminated encephalomyelitis; or is a spontaneous disease activated?

(iii) To what extent can this experimental disease be classed with disseminated sclerosis and disseminated encephalomyelitis in man?

Provocation with Forssman's Antibodies.

Jervis (1943) found that an injection of Forssmann's antibodies into the carotid artery of guinea-pigs was immediately followed by deviation of the eyes, nystagmus, and rotary movements of the body. The histologic changes have been followed from hour to hour and they consist in severe circulatory disturbances, bleeding, swelling of the endothelium, perivascular edema, diffuse damage to the ganglion cells, and non-perivascular demyelination. In the less acute cases, i.e. animals killed several days after the reaction has subsided, the degeneration of the ganglion cells was very small, while the axis cylinders were more affected, showing severe demyelination and deposition of neutral fat in the fat cells. Cellular infiltrations were scant. In the control animals, which were injected with starch granules, the clinical signs were indefinite, but similar; histologically, there were areas of anemia and hyperemia and small hemorrhages, but no local degeneration in the parenchyma. Thus, a purely anaphylactic reaction in the central nervous system can produce varying degrees of localised degeneration. It should be noted that in the many experiments (50 guinea-pigs) only few infiltrations

were found. Either the reaction in the ganglion cell can be rapidly reversed, or it is less severe than that in the fibre. Some part is certainly played by circulatory disturbances, though these may not be primary.

Provocation with Brain Substance.

Allergic experimental encephalomyelitis can be produced in guinea-pigs, rabbits, dogs and monkeys. Rats and mice have been tried, but without success. Analogous experiments have been made on humans, if one may cite Pasteur's rabies vaccine, which has also been used in many experiments on monkeys. In humans, about 14-21 injections of the vaccine are given for the immunization. In one in 4-5,000 this causes disseminated encephalomyelitis, but in some of these it has been possible to demonstrate rabies virus in the central nervous system; the frequency of the virus in the central nervous system of those who have been injected with vaccine but have not been ill, is of course not known. Observations made after general small-pox vaccination may perhaps be regarded as analogous. After small-pox vaccination, the virus can be demonstrated in the central nervous system and in the rest of the organism (see *Fog*, 1948), without signs of encephalomyelitis.

Freund's Adjuvant Technique.

In all the experiments made on animals it was at first only possible to find antibodies to brain in rabbits. In other species they could only be found when a very special technique was used. This special technique was first used by *Kabat, Wolf & Bezer* (1947) on monkeys, and independently by *Morgan* (1947). The technique was described by *Freund & McDermott* (1942). It is based on the observation that tuberculous guinea-pigs injected with various antigens unrelated to the tuberculosis, produce more antibodies than non-tuberculous guinea-pigs similarly treated. If albumen or horse

serum is injected into tuberculous foci, the sensitization to these antigens is quite different from that seen in non-tuberculous guinea-pigs; the cutaneous reaction is greater and lasts longer; it may be necrotic. This was confirmed by other workers. If paraffin oil is now added to the antigen-bearing tubercle bacilli, the severity of the lesion increases, as also the sensitivity to tuberculin. The paraffin oil is thought to increase the cellular reaction produced by the tubercle bacilli, by protecting them from destruction and thus favouring the sensitization and antibody formation. If lanolin is also added, the effect is still more marked. In U.S.A. aquaphor, a special lanolin substance, is used. Lanolin should delay the destruction of the antigen. This technique is called "Freund's adjuvant technique". It appears to have been generally accepted as a means of producing vigorous and lasting antibody formation against a number of antigens: horse serum, diphtheria toxoid, paradysentery, typhus vaccine, influenza virus and also against pollen allergens (see further *Morgan* (13)). It was when using this technique that *Morgan* "accidentally" induced encephalomyelitis in monkeys, during an attempt to produce particularly vigorous antibody formation against poliomyelitic spinal cord.

The introduction of Freund's adjuvant technique caused a revolutionary change in methods of investigating experimental encephalomyelitis. While *Rivers, Sprunt & Berry* (4) had been successful in only 2 out of 8 monkeys (after 50 injections), *Rivers & Schwentker* (5) in 6 (7) out of 8, (after numerous injections over a period of several months), and *Ferraro & Jervis* (1940) in 6 out of 7 (only after 3-weekly injections for from 4 to 13 months), *Morgan*, using Freund's technique, was able to produce both clinical and histologic changes in 26 out of 41 monkeys with only 3 (or, in some cases 2) injections, and after a much shorter latent period. *Kabat, Wolff & Bezer* (12) succeeded in 17 out of 19 monkeys, between 20 and 30 days after the first injection; *Ferraro & Cazulo* (1948) used from 1-9 injections, also in monkeys; *Jervis & Koprowski* used 3 injections in guinea-pigs, and were

successful with 24 out of 30 animals. *Morrison* (1948), using one injection distributed on the four feet, succeeded with 9 out of 10 rabbits. In our own investigations only 2-3 injections were used in rabbits and 2-4 in dogs; of these, one dog developed encephalomyelitis, and another dog developed acute ataxia after 4 injections.

Thus, as has already been stated, it was possible, when using this technique, to demonstrate antibodies in animals other than rabbits. *Kopeloff & Kopeloff* (1944 and 1947) found about the same concentration of antibodies, of about the same size, in both rabbits and monkeys, by using a standard technique. In rabbits, however, the adjuvant technique does not raise the titre. Pareses could be caused by a single injection. If tuberculin was omitted, the effectivity was reduced. Serologically crossed immune reactions, between brain tissue and testes and kidneys, were found. Guinea-pigs gave positive cutaneous reactions to rabbit brain adjuvant but not to guinea-pig brain. Guinea-pigs injected with boiled rabbit brain, which is just as effective, gave positive cutaneous reactions to rabbit testes. If neurokeratin emulsion was injected, a positive cutaneous reaction developed to rabbit or calf brain. Guinea-pigs injected with guinea-pig brain, with or without an adjuvant, never gave positive skin reaction to guinea-pig brain. In rabbits, no correlation was found between the antibody titres and the presence or absence of pareses.

Morgan (13), *Kabat, Wolf & Bezer* (12) and *Freund, Stern & Pisani* (21) have all tried passive serum antibody transference from sick to healthy monkeys and other experimental animals, with negative results.

Although the serologic aspect is by no means understood, it seems definite that in monkeys also it is possible to provoke the formation of an antibrain substance by a technique capable of accelerating and intensifying disseminated encephalomyelitis. It seems that antibodies cannot be transmitted passively. An immune relationship is found between the testes and kidneys, and the brain, but not between other organs and

the brain. Thus *Kopeloff & Kopeloff* believe that the neurologic findings seen in these investigations may arise from a sensitizing process. Cutaneous allergy can be demonstrated in guinea-pigs after immunisation with rabbit brain or testes.

The Experimental Disease.

The nature of the disease produced by the injections is not known. In rabbits it is most difficult to understand. *McCartney* (1924) found histologic encephalitis in 50 per cent of 372 non-paretic rabbits. Demyelination, however, was not found, and *Morrison* (18) thinks therefore that the experimental disease is to be distinguished from spontaneous encephalitis. Fifteen per cent of *McCartney's* animals showed quite specific and easily recognizable changes. Rabbits infected with e.g. colds, coccidiosis, pneumonia, abscesses etc., were found to undergo considerably more encephalitic changes; histologic encephalitis was found in 75 per cent of rabbits with colds.

It is still more difficult to understand the findings in paralysed animals with normal histologic appearances. *Kopeloff & Kopeloff* (1947) and *Morgan* (13) examined peripheral nerves, using the sciatic nerve, and found no changes.

Experiments on monkeys have been more encouraging. In all the experiments there was also a large control material of normal animals. These always showed negative findings. Similarly, negative findings were also obtained when other animals and monkeys were injected, either intramuscularly or intracerebrally, with brain emulsion from the sick monkeys. Injections of the extracts of other organs and of peripheral nerves into monkeys, have also always given negative results. *Morgan*, in particular, had a large control material.

There was a definite correlation between the clinical and pathologic pictures in the monkeys. Two of *Morgan's* monkeys were clinically negative and one of *Rivers & Schwentker's* (6). Paretic monkeys without pathologic findings have not been seen.

The pathologic changes have been found only in the brain and spinal cord, never in other organs, apart from those of the monkeys with tuberculosis.

Spontaneous disseminated encephalomyelitis occurs in rabbits, dogs and monkeys; in dogs and monkeys, the pathologic changes of the experimental disease closely resemble those of the spontaneous form. In monkeys, the spontaneous disease may be endemic, and is often related to tuberculosis, though not always. It is interesting that tuberculosis was found in several cases of experimental allergic encephalomyelitis. The many negative results in the control animals make it unlikely that the disease was really the endemic spontaneous form. The nature of the spontaneous disease is very puzzling; it is illustrated by the nomenclature. Thus, *Scherer* (19) speaks of spontaneous encephalomyelosis. Further studies of this condition are badly needed.

The Antigen.

Brain and spinal cord have been used as antigens. The preliminary results suggest that it is immaterial whether the brain used is homologous or heterologous. *Morrison*, however, found that the changes were much more severe when a heterologous antigen was used.

It is interesting that the antibodies produced in both rabbits and monkeys are much more organ than species specific. They are not, however, entirely organ specific. Control microscopy of the brains used as antigens has shown that brain which is microscopically normal is a satisfactory antigen. More antigen is present in the white matter. Emulsions made from peripheral nerves or neurokeratin do not cause pareses, even when used with adjuvant. Kidney emulsions can produce pareses in guinea-pigs; testes emulsions cannot.

Clinical Aspects.

Finally, there remains the question of the possible relation between the experimental disease in animals and disseminated encephalomyelitis and disseminated sclerosis in man. For a very long time attempts have been made to define more exactly the clinical disease termed disseminated sclerosis; but so far, such a definition—clinical or pathologic—has not been possible. A recent clinical investigation by *Thygesen* (1947) showed that in many cases a clinical distinction can be made according to the course of the disease; an intermittent is distinguished from a more steadily progressive type, and this differentiation makes certain prognostic distinctions possible, in that the prognosis of the intermittent type is much better than that of the insidious progressive type. *Thygesen* believes that severe widespread signs, with a relatively short history, especially in young persons, suggests a bad prognosis. However, in some cases it is extremely difficult to classify the patients under either group, and they are regarded as being of mixed type.

Studies of the course of the disease in animal experiments are therefore of interest. No conclusions can be made from studies carried out before the adoption of an adjuvant technique, for in these the injections were continued until the animals died or were killed. Now, however, when the injections are stopped either before or shortly after the first signs appear the different courses can be distinguished.

In rabbits, both a swift steady progress to death, occurring within a few weeks, and an intermittent course are seen. The animals may develop new symptoms from one day to another; these symptoms may be very severe, as in one of our own experiments; or they may progress for a number of days up to 1-2 weeks, and then remain stationary, fluctuate or regress. In our animals we have not seen real intermittent signs of varying localisation (*Fog & Hertz*). We now have rabbits which were severely paretic and survived up to 11 months. Some are quite without signs of disease; in others the condi-

tion is stationary. We have not seen late relapses¹. It has not been possible to differentiate between pyramidal and co-ordinating types. The most definite signs are pareses or paralyzes. Whether ataxia is also present, is difficult to estimate. Paralysis of a rabbit's hindquarters interferes so much with its postural stability that a disturbance of co-ordination may easily be suggested. We have not seen the other forms, ataxia or nystagmus, described by *Morrison*¹. The pareses are frequently flaccid and include a severe sphincter paralysis. Spasticity is also seen. No definite changes have been seen on ophthalmoscopy. It is worth noting that animals lose weight in the active stage; loss of weight is also frequently seen in the acute phase of human disseminated sclerosis. The general condition may be affected, though usually only in the quadriplegic animals.

Jervis & Koproński have given the following description of the course of the disease in guinea-pigs. In one group of 7 animals the symptoms progressed steadily until death occurred, 5-15 days after the first signs. In 5 animals the course was intermittent, with complete remission after the first attack, followed by death after relapse. Twelve animals had only one slight attack, or possibly slight intermittent attacks with vague signs lasting only a few days. The animals were killed 5-6 weeks after the signs had disappeared.

In their experiments on monkeys, *Kabat, Wolff & Bezzer* (12) found that in 2 out of 17 the course was definitely remittent; in others it progressed more steadily until the animals either died or were killed. *Ferraro & Cazzulo* (16) injected 19 monkeys. Six survived the acute attack. The course was described as progressing until death, or fluctuating, i.e. remittent. *Morgan* (13) did not differentiate between the different courses. Most had general signs. These began 2½ to 5 weeks after the injection and reached their peak between the 2nd and 4th weeks. Occasionally there was fever. There was no eosinophilia. *Kabat, Wolff & Bezzer* counted the cells in the cerebrospinal fluid. They found 2, 18, 107, 254, and

667 cells, which is surprisingly few in view of the cellular infiltration, seen histologically.

Thus, as far as its course is concerned, experimental allergic encephalomyelitis is comparable with human disseminated encephalomyelitis, in which the same both progressive and more remitting forms are wellknown. Fundamentally it also resembles disseminated sclerosis, though in a shortened form. The boundary between acute disseminated encephalomyelitis and disseminated sclerosis is well known to be so ill-defined that a sharp distinction is impossible. (*Fog*, 1948). The general reaction, with loss of weight, possibly slight fever and moderate pleocytosis, is the same.

Since the adjuvant technique has only been used for a few years, the future should produce further data on the later course of the experimental disease.

The analysis of the localisation of the signs is also interesting. It is characteristic of all the monkey experiments that the signs arise almost exclusively from the cerebrum, cerebellum, brain stem and optic apparatus. In man, the spinal cord and then the optic system are the favourite sites of origin. This will be further discussed later on.

Pathologic Anatomy.

Finally, the pathologic anatomy must be described.

Pathologically, the experimental disease is a meningo-encephalitis. The most striking changes are the infiltration in and under the meninges and round the vessels. The parenchymatous changes are perivascular, predominatingly round the veins. The cellular infiltrations have a disseminated distribution.

In monkeys the spinal cord and its coverings are only rarely affected, and if affected show only mild changes. In guinea-pigs, however, subpial and perivascular changes in the spinal cord predominate (*Jervis & Koprowski*). *Freund, Stern & Pisani* (21), however, have described a diffuse meningeal thickening over the whole central nervous system

in their guinea-pigs. In rabbits, the lesions appear to be evenly distributed throughout the brain and spinal cord.

In the so-called acute disseminated encephalomyelitis of human beings a similar variation of distribution of the lesions in the brain and cord is seen. In the more protracted forms, which merge with disseminated sclerosis, both the brain and spinal cord are found to be affected on post mortem examination, but purely cerebral and cerebellar attacks are well-known to be acute in the course of the chronic disease.

Degenerative Changes.

In the experimental disease, one sees infiltrations corresponding to the parenchymatous degeneration observed in cases where the infiltrations go beyond the vessel sheaths. In both acute disseminated encephalomyelitis and disseminated sclerosis, are seen the well-known perivascular demyelinations which combine to give bigger foci.

Demyelinations, though varying in degree and extent, are described for all monkey experiments. In rabbits also areas of demyelination in the spinal cord, 2-3 times the vessel's diameter, were described by *Morrison*. In our rabbit experiments we also found definite perivenous demyelinations, but only very rarely. However, these investigations are by no means complete. In guinea-pigs, *Jervis & Koprowski* found only slight demyelinations. In our experiments on dogs the demyelinations were very marked. With demyelination occurs neutral fat formation.

The animal experiments justify the preliminary conclusion that the frequency of the degeneration of the myelin depends on the phylogenetic development of the species, but that the pareses show no logical relation to the demyelinations. On the other hand, the antigenicity depends on the degree of myelination.

The degree of axis cylinder degeneration varies. Often the ganglion cells are strikingly spared.

Vascular Changes.

Vascular changes consist in dilatation, a tortuous course of the vessels, endothelial swelling, and frequently hemorrhages, usually in the form of petechiae, though sometimes massive. Thromboses were seen only rarely by *Kabat, Wolf & Bezer*, frequently by *Freund, Stern & Pisani*. *Ferraro & Cazzulo* emphasise the absence of thromboses. *Ferraro & Jervis* also state that they found no fibrin deposits or platelet agglutinations; *Morrison* describes different degrees of occlusion of the vessels, mostly in the form of endothelial or subendothelial proliferation.

The Infiltrations.

It is noteworthy that all the published works about experimental allergic encephalomyelitis emphasise that, pathologically, the disease is characterized by its infiltrating nature. The infiltrations do not respect the limiting membrane of the glia, but cross it into the parenchyma. This in itself is not particularly surprising, since the infiltrations are also marked in acute disseminated encephalomyelitis and in acute attacks of disseminated sclerosis. The histologic characteristic, which differentiates the experimental from the human disease, is the type of infiltration.

It is a general rule that both disseminated sclerosis and its acute forms consist of a non-suppurative disseminated encephalomyelitis. This means that true tissue infiltrations, with lymphocytes, plasma cells and leucocytes, are never seen. This has been pointed out again and again. The problem has been particularly studied by *le Roy von der Maeder* (1931), who examined a series of cases of disseminated sclerosis from this point of view. True isolated infiltrations with lymphocytes, leucocytes or plasma cells were never seen. They were only rarely seen in the 100 cases of acute disseminated encephalomyelitis which I discussed in my thesis (1948). Markedly infiltrative disseminated encephalomyelitis is occasionally seen in human material, but it is rare (*Hassin* (1938)).

In the animal experiments, leucocytes, lymphocytes, plasma cells, histiocytes, and, (as in man), microglia, are found in the vessel sheaths and in the disseminated foci. Eosinophilia is not marked when the adjuvant technique is used, though it was observed by *Ferraro & Jervis*, *Rivers & Schwentker* (6) and *Rivers, Sprint & Berry* (4). Giant cells were described by *Rivers & Schwentker* (6), *Ferraro & Jervis* (15) and by *Morrison* (in one of his rabbits), i.e. in the experiments when eosinophilia was also seen. Giant cells are frequently seen in acute disseminated encephalomyelitis in man (*Fog* (11)).

The histologic picture has a quite typical appearance, because of the epitheloid cells which are frequently seen and are easily recognisable; sometimes rather large infiltrations with these cells have been described. I do not believe that I have seen these cells described, at any rate, not in such large numbers, in disseminated encephalomyelitis or disseminated sclerosis.

Thus one may say that, pathologically, experimental allergic encephalomyelitis is characterized by its infiltrations, and that these infiltrations contain cells which are rarely seen in the human diseases. They thus give a characteristic picture of the experimental disease. They are found regardless of the species of animal.

Neuroglia.

Obviously, the neuroglial changes are of particular interest when one is discussing disseminated sclerosis. In this connection it is the macroglial reactions which are of particular interest. It might be expected that they would show few changes in the short term experiments, but if one may draw conclusions from human pathology, this is not justified. The central nervous system is able to respond very quickly with macroglial changes. In the material described in my thesis, there were marked macroglial reactions in 30 cases of acute

disseminated encephalomyelitis, lasting less than one month, while in 31 out of 100 cases, with courses lasting between 1 month and 2 years—in one case even 4 years—only slight macroglial changes were seen. Thus, the macroglia, like mesodermal tissue, vary considerably in their reactivity, and this is obviously determined by some other factor than time.

Most of the monkey experiments lasted less than one month. Generally, the astrocyte reaction was slight or moderate. Fibre formation was usually absent. *Freund, Stern & Pisani* describe granuloma-like accumulations of astrocyte-like cells in guinea-pigs.

In *Ferraro & Jervis'* experiments the disease lasted 12-90 days. They found proliferative changes in the glia round the foci of degeneration, and described foci with hyperplastic and hypertrophic glial changes containing numerous glial fibrils (cf. their fig. 6, Holzer stain) as well as more diffuse zones, not related to the vessels, with progressive macroglial reactions in the macroglia. *Morrison* described in rabbits a macroglial reaction as a border astrocytosis round the degeneration focus, different from that seen in the typical sclerotic plaques in man. He points this out himself.

The changes in the central nervous system in *Ferraro & Cazzulo's* so-called "chronic" experiments are very interesting. 2 monkeys, which had been ill for 77 and 105 days respectively, were examined. The monkey which had lived 105 days showed definite and plentiful astrological reaction, but no fibre formation could be found with Holzer's stain. In the other animal, which had been ill for a shorter time, true glioses were found. These 2 cases have a further interest. In the first monkey, which had been ill 105 days and showed no glioses, the pathologic changes were almost exclusively throughout the optic system, from the optic nerves via the optic tracts and geniculate bodies to the occipital lobe; in the other monkey, the changes were mainly in the brain stem, where the glioses described were found. In a third monkey, which had been ill for only 29 days, there was a generalised

neuroglial hypertrophy, with both progressive and regressive changes and also fibrillary gliosis. No correlation was seen between the degeneration and the glial proliferation.

We are familiar, clinically, with cases of disseminated encephalomyelitis in which the changes are confined to the optic system (as in the monkey described), and the spinal cord—neuromyelitis optica as it is called. This disease is characterized in a number of cases by lack of regular gliosis, in spite of its prolonged course. Admittedly, in man there are also changes in the spinal cord, but the signs from the optic system and from the cord progress quite independently of one another. There have been heated discussions on how far this disease may be due to a particular specific agent. In these animal experiments, similar clinical and pathologic changes have been seen, produced by the same agent as that which, in other animals of the same species, caused changes in other parts of the brain, and induced the formation of glioses. It should also be mentioned here that some of *Kabat, Wolff & Bezer's* monkeys showed changes mainly confined to the optic system. Whether these animals showed the lack of glioses, is not mentioned.

One must of course guard against drawing too wide conclusions from differences in the degree of mesodermal reaction and variations in the amount of neuroglial reactions.

The plentiful mesodermal infiltrations are seen in all animal species; the epithelioid cells characterize the experimental disease. It is very possible that the experimental disease is related to one or more human diseases by a common factor, which works physiologically and pathologically in the same way. The same cause can have widely differing effects on an organism, and the same reaction may be produced in many other ways than described here. It is the comparisons which can be drawn between the experimental diseases, concerning the signs, course and localisation in the central nervous system, and the detailed histology which are of interest.

It remains to be seen whether it is possible to produce in experimental animals disseminated sclerosis with a prolonged

course lasting for years¹ and the corresponding characteristic changes. And one may expect an elucidation of the mechanism of the experimental disease, and of the nature of the antigen, the demonstration of a tissue sensitization in patients with disseminated sclerosis and disseminated encephalomyelitis, and a more thorough study of the spontaneous diseases in animals.

S U M M A R Y

In recent years it has been possible to produce disseminated encephalomyelitis in a number of experimental animals by repeated subcutaneous and intramuscular injections of brain substance. By means of a special technique (Freund's adjuvant technique) it is possible to reduce the number of injections to very few. With this technique, the antibody formation is intensified and activated. In some animal species specific organ antibodies are found in the blood, but passive transmission has not been successful. The antigen is thought to be contained in the white substance, but its nature is not known.

In its clinical manifestations, course, localisation and pathology, the experimental disease is reminiscent of the acute forms of disseminated sclerosis. Pathologically, the experimental disease differs from disseminated sclerosis in its predominatingly infiltrating character, with lymphocytes, plasmacytes and epitheloid cells. Eosinophilia is seen mainly when Freund's adjuvant technique is not used.

Experimentally it is possible, by using the same species of animal and the same technique, to produce changes in the brain that are reminiscent sometimes of disseminated sclerosis and sometimes of neuromyelitis optica, as far as the localisation of the changes and the type of neuroglia reaction are concerned.

¹ Since this article was concluded, one of our dogs, without further injections, had a sudden relapse, several months after spontaneous remission from an acute ataxia. The symptoms were ataxia again and cerebellar fits, from which he died suddenly.

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LES MASTOIDITES RECIDIVANTES DU POINT DE VUE ALLERGIQUE

Par

le Dr. ALFREDO ANTONIO GALLO

La question des Mastoïdites à Récidive (= M. R.) a fait déjà l'objet d'étude par plusieurs spécialistes, à partir de 1901, lorsque Israël de Turin publia la première communication sur 5 cas. Les M. R. étaient alors si rares que souvent on signalait des cas isolés. En raison de cette rareté elles furent mises même en doute. (Voir Frey : Sur la question des prétendues M. R.).

Peu à peu l'intérêt des otologistes devint si aigu, que la question fut posée à l'ordre du jour du Congrès O. R. L. de Vienne en 1912.

La première étude organique sur l'argument ne parut qu'en 1917 par Tarneaud qui traita de l'anatomie pathologique, de la pathogénèse et de la thérapie des M. R.

Tarneaud insistait surtout sur le fait que dans la M. R. les lésions osseuses sont exceptionnelles, et que la simple incision avec drainage, sans curettage, suffit dans la plupart des cas.

En 1926 Portmann et Retrouvey reprirent la question en se demandant tout d'abord : « La M. R. existe-t-elle ? » Ces auteurs proposèrent le terme plus exact de Mastoïdite opérée récidivante et acceptèrent beaucoup d'idées de Tarneaud. Ils distinguèrent la rechute de la récidive, en entendant par rechute le retour d'inflammation quand l'otite n'est pas encore entièrement éteinte, et par récidive une nouvelle mastoïdite se manifestante *longtemps après* la guérison clinique et anatomique de la mastoïdite déjà opérée.

D'après Portmann on peut considérer une mastoïdite comme guérie si la cicatrice rétroauriculaire est normale, légèrement dépressée (si guérie par seconde), sans croutes ni fistules, indolore à la pression, s'il n'y a plus d'écoulement d'oreille, ni d'exsudat dans la caisse, si la M. T. est cicatrisée, l'ouïe

normale (Portmann). À mon avis cette guérison est apparente. Elle peut devenir définitive après plusieurs mois, mais il peut aussi arriver (et il arrive souvent) qu'un enfant, qui a quitté l'hôpital dans ces conditions, y retourne après quelques jours, quelques semaines, quelques mois avec son otite ou sa mastoïdite. Il ne s'agit évidemment pas de récurrence, mais de rechute, c'est à dire que l'otite n'était pas entièrement éteinte, malgré toute apparence ; ou, ce qui est peut-être mieux compréhensible, que le procès de guérison dans la cavité opératoire était seulement à sa première étape : celle de granulation. Avant qu'elles puissent s'organiser en tissu fibreux, plusieurs mois devront s'écouler. Afin de prévenir une récurrence Portmann et Retrouvey conseillent d'évider largement et minutieusement toute la mastoïde et, en second temps, de bonifier les voies aériennes supérieures (adénoïdes, tonsilles, sinusites etc.).

En ce qui concerne le procès de guérison d'une mastoïdite opéré, on en savait fort peu en 1908, quand Frey (Wien) écrivait : « ... bedauert dass wir über die Regeneration des Warzenfortsatzes nach der Trepanation noch so wenig wissen ; es ist ja gewiss möglich dass die Heilung in verschiedenen Fällen in verschiedener Weise und insbesondere, was die Bildung soliden Knochens betrifft, in verschiedener Zeit abläuft ». Ensuite, au fur et à mesure que les observations se firent plus nombreuses, on arriva avec Mauret à cette conclusion : qu'une mastoïdite opérée, en traversant les phases de tissu de granulation, de tissu fibreux, de tissu osseux, tend à reprendre sa conformation originaire, c'est à dire plus ou moins pneumatique, ou plus ou moins compacte. Le tableau clinique de la récurrence est dicté par la phase de reconstruction dans laquelle elle se manifeste. Se manifeste-t-elle quand la mastoïde est entièrement reconstruite, les symptômes seront les mêmes que ceux d'une mastoïdite primitive ; toutefois l'extériorisation sera plus facile à cause de la moindre résistance de la corticale externe. Se manifeste-t-elle avant le procès d'ossification, les symptômes généraux seront peu accentués, la douleur spontanée très faible, celle provoquée plus forte et plus précoce que dans la mastoïdite primitive. Très rapidement la peau devient rouge, gonflée ; il s'agit tout court d'un abcès dans la cicatrice. Parmi ces types extrêmes il y a qui correspondent à une partielle reconstruction osseuse. Une M. R. peut se manifester à une époque très variée après l'opération. Je ne parlerai pas de celles qui arrivent dans les 2—3 premiers mois, parcequ'elles doivent être considérées comme des rechutes ou fausses récurrences. Les vraies M. R. se manifestent surtout au cours des deux premières années après l'opération (60 %), et surtout chez les enfants ou dessous de 10 ans (62 %). Les patients qui font une M. R. au cours de la première année après l'opération font ensuite d'autres récurrences, jusqu'à 6 fois. Elles sont caractérisées par une extrême bénignité. Souvent elles n'arrivent pas à la phase suppurative. Chez les adultes la M. R. se manifeste après plusieurs années, jusqu'à 20—25 ; elle est en général unique.

Concernant la précocité ou la tardivité de la première opération en rapport avec les M. R. nous avons la statistique de Scholz (Frankfurt a. Ma) publiée en 1936 :

Mastoidectomies	Temps d'opération	Récidives
125	après la 3 ^{me} semaine	7 %
153	1 ^{re} —3 ^{me} semaine	7 %

Pour la Clinique de Lund nous avons :

Age de l'otite	1-21	22-30	31-90	?	(opérés ailleurs)
Cas N°	27	7	9	18	
Récidives N°	43	7	11	29	

C'est à dire que 47 % des récidives se sont vérifiées chez des patients opérés précocement, 20 % chez patients opérés tardivement. Je dirai ensuite (page 9) comment ces pourcentages doivent être interprétés.

CAUSES DES RÉCIDIVES

La plupart des otologistes sont d'accord pour admettre que les récidives ont leur origine :

- 1) dans une opération incomplète ;
- 2) dans les maladies infectieuses de l'enfance, telles que la scarlatine, la rougeole etc ;
- 3) dans l'état général du sujet : lymphatisme, hypertrophie des tonsilles et des adénoïdes, rhumes, angines, *idiosyncrasie, troubles digestifs*.
- 4) dans la brièveté de la trompe d'Eustache chez les enfants, et dans la largeur de l'aditus après la mastoïdectomie.

Selon Bruzzi (Naples) les récidives sont particulièrement fréquentes : a) dans la suture rétroauriculaire complète ; b) dans les mastoïdites opérées non suturées, lorsque, par trop de hâte de la part de l'opérateur, les pansements ont été trop légers ; la cavité opératoire se remplit dans ce cas de la surface vers le fond, au lieu du fond vers la surface, en renfermant ainsi une cavité purulente, qui tôt ou tard provoquera non seulement une récidive, mais aussi de nouvelles lésions ostéitiques.

Julius Lempert, convaincu que la cause de récidive réside dans le procédé opératoire de Schwartze, proposa une nouvelle méthode, c'est à dire la mastoïdectomie subcorticale. Voici, en original, le résumé de sa communication parue en 1929 dans « Monatschrift für Ohrenheilkunde ».

- 1) « Die subkortikale Mastoidektomie hinterlässt eine anatomisch stärkere Mastoide gegen als die Schwartzesche Mastoidektomie, weil viel weniger Gewebe in der ersteren als in der letzteren Operation geopfert wird.
- 2) Weil die oben angeführte Tatsache der postoperativen subkortikalen Mastoidektomie der Mittelöhrinfektion mehr Widerstandskraft bietet als die postoperative Schwartzesche.
- 3) Der Herd des geringsten Widerstandes für die Infektion bei der vollständig geheilten postoperativen Schwartzeschen Mastoidektomie ist das fibröse Bindegewebe, welches das Innere des Processus mastoideus mit der äusseren Wand der devitalisierten Haut und dem Narbengewebe füllt und auf diese Weise die frühere dicke äussere Wand des Cortex mastoideus ersetzt, welche mit gesundem Periost und Haut bedeckt war.
- 4) Der Herd des geringsten Widerstandes für die Infektion bei einer vollständig geheilten postoperativen subkortikalen Mastoidektomie ist die dünne hintere Epitelkanalwand, welche das einzige anatomische Gebilde ist, welches den Aditus von dem äusserem Gehörgang trennt. Diese dünne Hautschicht ersetzt die frühere äussere Wand der Cortex mastoideus mit ihrer Haut und ihrem gesunden Periost, welche die hintere knöcherne Gehörgangswand bildet.
- 5) Auf Grund der Tatsache, dass die Infektion immer den Weg des geringsten Widerstandes einschlägt, und dass die anatomische Ara die den geringsten Widerstand bietet, in den zwei postoperativen Regionen verschieden ist, muss natürlich eine Otitis med. pur. ac. bei einer postoperativen subkortikalen Mastoidektomie ein anderes Enderesultat haben als bei einer postoperativen Schwartzeschen Mastoidektomie ».

À l'appui de ses idées Lempert présentait deux statistiques, dont l'une sur 425 mastoïdectomies selon Schwartze, l'autre sur 425 mast-ect. selon Lempert. Dans le premier cas il eut 18 M. R., mais aucune dans le deuxième.

En 1938 Lempert ajoutait :

« A careful comparative study of the postoperative course, the convalescence, the period of healing and the ultimate end results obtained in the 1780 consecutive cases in which operation was performed by me through the endaural, antauricular surgical approach more than justifies my abandonment of the postauricular approach to the temporal bone ».

Pouvons-nous, après ces affirmations catégoriques de Lempert, considérer comme achevée la discussion sur les M. R. ?

Il y a deux remarques à faire :

- 1) Que toutes les mastoïdites aiguës ne sont pas justiciables de la méthode de Lempert. Même si on veut ignorer le magistral travail publié par Mouret en 1928 sur la systéma-

tisation de la mastoïde et sur la technique à suivre dans la mastoïdectomie (Acta Otolaryngologica 1928) on doit admettre que la méthode de Lempert ne permet pas l'exploration et l'ouverture de toutes les cellules mastoïdiennes, dont la persistance, si elles sont infectées, est cause si souvent de rechute, ou de complications, et que, par conséquence, si l'on veut en croire Lempert, on doit conclure que ses cas étaient tous non compliqués, et limités à l'antre et à ses environs immédiats.

2) Que la méthode de Lempert a pour but de créer le « locus minoris resistentiae » dans le conduit au lieu de celui sur la surface externe de la mastoïde. La route suivie par la récidue mène donc à la cicatrice rétroarticulaire avec la méthode de Schwartze et à la paroi postérieure du conduit avec la méthode de Lempert (voir 5) de ses conclusions).

En 1930 Alexander répondait ainsi à Lempert : « Rezidive von Mastoiditis nach Operation von aussen sind nicht so häufig als dass man sie einen Nachteil der Antrotomie von aussen betrachten könnte. Überdies haben sie in keiner Weise in der Operation von aussen ihre Ursache. Wenn sich bei der Mastoidoperation von aussen das Periost nach beendeter Operation wieder ausbreiten lässt, so bildet sich eine äussere Knochenschale als postoperative Korticalis aus. Unter diesen Umständen sind wir, weit besser als nach den membranösen Verchlüssen nach der Lempert-Operation in Gehörgang, vor einer Zurückfallseiterung bewahrt ».

J'ai cherché à donner un aperçu aussi complet que possible des idées dominantes au sujet de la M. R. Ces idées n'ont pas fait d'appréciables progrès dans ces dernières 20 années, tandis que la technique opératoire s'est de plus en plus affinée et les ressources thérapeutiques se sont enrichies, grace surtout aux sulfamides et à la pénicilline. La radiographie, pratiquée systématiquement, décèle d'avance toute lésion osseuse et guide, pour ainsi dire, la main du chirurgien. L'antrotomie a été abandonnée pour une mastoïdectomie aussi radicale que les lésions le demandent. On réalise la prophylaxie des récides en bonifiant les voies aériennes supérieures ; mais tout cela n'a pas empêché que les récides continuent à se manifester dans la même mesure qu'auparavant.

Si nous observons les chiffres de ces dernières années, nous remarquons même une tendance à augmenter, en même temps que les mastoïdectomies diminuent. Nous avons en effet 12,5 % de M. R. en 1946, 15,5 % en 1947, 26 % en 1948. L'avenir nous dira s'il s'agit là d'un phénomène transitoire.

La question est donc toujours actuelle et je me propose de l'examiner à nouveau.

Ce travail a pour but de voir :

1) Si l'évidement incomplet de la mastoïde, les maladies infectieuses, et plus précisément la scarlatine et la rougeole, les affections des voies aériennes supérieures peuvent être facteurs de M. R.

2) Si la constitution allergique peut être facteur de M. R.

Cette dernière idée appartient au Prof. G. Dohlman, Chef de la Clinique O. R. L. de Lund. Il a voulu me la confier, et je lui exprime ici ma gratitude.

En considérant la confusion qu'on fait souvent entre vraies et fausses M. R. il faut tout d'abord en donner une *définition*.

La vraie M. R. est l'inflammation aiguë simple, muqueuse ou purulente, qui se vérifie comme complication d'une otite aiguë dans une mastoïde opérée depuis au moins trois mois et parfaitement guérie cliniquement, anatomiquement, fonctionnellement. Elle est donc une nouvelle mastoïdite tout à fait indépendante de la première.

La fausse M. R. ou rechute, est le retour d'inflammation qui se vérifie pendant la période de convalescence ou à peu de distance de la guérison de la blessure opératoire, provoqué souvent par des cellules infectées ou par des maladies infectieuses intercurrentes. Les abcès dans la cicatrice sont de vraies M. R.

Quelques statistiques.

	date	période	mast. ectomies	M. R.	%	
Hôpital communal de						
Copénague	1911	1905—10	225	21	9	
Ech	1926	1922—25	625	25	4	
Lempert	1930	?	425	18	4	Méthode Schwartz
„	1930	?	425	0	0	„ Lempert
Scholz	1936	?	278	20	7	
Hôpitaux suédois.						
Malmö		1931—46	1818	138	7,6	
Lund		1931—48	1765	205	11,5	
Stockholm (Sabbatsberg)		1931—40	2028	353	17,4	
Göteborg		1933—44	1779	91	5,1	Clinique O.R.L.
Göteborg		1933—44	686	57	8,3	Section chirurgie d'enfants.
Uppsala		1931—45	1792	143	8	

Ces statistiques nous donnent une idée très imprécise sur les récidives. En effet :

- 1) nous ne pouvons pas juger s'il s'agissait là de vraies récidives ou de rechutes ;
- 2) nous ne savons rien du nombre de récidives qui se sont vérifiées chez le même patient ;
- 3) nous ne sommes pas renseignés sur l'âge des patients ;
- 4) en ce qui concerne la deuxième statistique de Lempert, nous demeurons dans le doute si vraiment avec sa méthode il ait réussi à éviter toute récidive, ou si les récidives, au lieu de s'extérioriser sur la surface externe de la mastoïde, se soient extériorisées dans le conduit ;
- 5) enfin nous ne sommes nullement renseignés sur les causes des récidives ou sur les circonstances qui les accompagnaient.

En ce qui concerne les statistiques suédoises, elles compren-

nent aussi les récidives (abcès dans la cicatrice) qui ont été opérées ambulatoirement. Voici « in extenso » la statistique de Lund.

Hôpital de Lund. Clinique O.R.L.

	D'après les rapports officiels			Après sélection des rechutes	
	Mastoïdec- tomies	Non guéries	Récidives	Rechutes	Récidives
1931	128	2	7	4	3
1932	70		9	6	3
1933	86	2	7	7	0
1934	118		30	24	6
1935	157	10	5	1	4
1936	134	20	12	7	5
1937	121	3	10	6	4
1938	110		17	12	5
1939	106	5	17	7	10
1940	78		12	6	6
1941	66		13	5	8
1942	56			0	0
1943	115		15	13	2
1944	137		12	11	1
1945	83		7	4	3
1946	88		12	1	11
1947	97		15	0	15
1948	15		5	1	4
	1765	42	205 = 11,5 %	115 = 6,4 %	90 = 5,1 %

ANALYSE

La matière que je vais analyser consiste dans les M. R. qui ont été soignées dans la Clinique O. R. L. de Lund dans la période janvier 1931—décembre 1948. Sous cette diagnose figurent, dans les rapports annuels, 205 cas. Après un examen minutieux, conformément à la définition donnée auparavant, ces cas se sont réduits à 90 sur 61 patients. Puisque le total des mastoïdectomies est de 1765, il en suit un % de 5,1. Si nous considérons cette statistique dans deux sous-périodes : 1931—45 et 1946—48, nous avons les valeurs suivantes :

période	mast. ect.	moyenne par an	M. R.	%	No pt.	traitement soulfa pénicill.	
31—45	1565	104	60	3,9	44	3	0
46—48	200	66	30	15	17	16	7

Nous voyons donc une claire tendance vers une augmentation des M. R., qui coïncide avec l'emploi systématique des antibiotiques, des sulfamides en particulier. Cette tendance coïncide aussi avec la remarque que plusieurs ont faite récemment, à savoir que les otites aiguës traitées avec les antibiotiques ont un haut % de récidives. Le matériel et la période qui font l'objet de ce travail sont trop limités pour me permettre d'en tirer une conclusion quelconque. L'observation me semble toutefois digne d'être signalée.

Voici maintenant des tableaux dans lesquels j'ai groupé les données les plus intéressantes.

1)	Sexe	No pt.	No M.R.
	m.	30	46
	f.	31	44

2) Âge des patients à la première opération :

Âge: 1-11 mois	1-5 a.	6-10 a.	11-20 a.	21-75 a.
N° pt. : 3	20	17	10	11

3) Âge (en jours) de l'otite à la 1^{re} opération :

Âge:	1-21	22-30	31-90	?
N° pt. :	27	7	9	18
N° M.R.	43	7	11	29

La plus grande fréquence de M. R. chez les patients précocement opérés ne doit pas se mettre en rapport avec la précocité de l'opération, mais plutôt avec l'âge du sujet. En effet chez les enfants la mastoïdite arrive à maturité plus vite que chez les adultes, et le tableau 7 nous dit que c'est chez les plus jeunes que les M. R. arrivent avec plus de fréquence (62 %).

4) Époque des M.R. après la 1^{re} opération :

1 ^{ère} année	2 ^{me} année	3 ^{me} a.	4 ^{me} a.	5 ^{me} a.	6-10 ^{me} a.	après 10 ans
N° 19	30	9	6	8	13	5

5) Âge des M.R. à leur entrée en clinique :

2-7 jours	8-14 jours	+ 2 semaines	?
36	13	7	34

6) Mono-et plurarécidives :

1 fois (3 bilatérales)	2 fois (2 bilatérales)	3 fois	4 fois (2 bilatérales)
47	7	6	1

7) Distribution de M.R. selon l'âge :

1-11 mois	1-5 a.	6-10 a.	11-20 a.	21-75 a.
0	20	36	18	16

Les M. R. sont plus fréquentes chez les jeunes patients. Selon Portman et Retrouvey c'est parceque les mêmes causes qui ont provoqué la première mastoïdite provoquent aussi les M. R. (rhino-pharyngites, fièvres éruptives, lesquelles jouent un très grand rôle dans la pathologie de la première enfance.) Á ces facteurs Lacy (Kansas) en ajoute des autres : « Any debilitating disease will tend to make a child more susceptible to reinfection. Nutritional disturbances are commonly noted in these cases and in part account for the poor regeneration of bone and delayed healing after the primary operation ». Je pense que la théorie allergique de Dohlman sur les otites des enfants peut bien s'appliquer aussi aux M. R. Selon Dohlman l'extrême fréquence des otites chez les plus jeunes parmi les enfants dépendrait d'une sensibilisation allergique de la muqueuse de la caisse, provoquée par le lait de vache administré soit comme laitage artificiel, soit pendant le sevrage. Ce lait, qui vient ingéré d'une façon inaccoutumée et en quantité souvent excessive, agirait comme corp étranger sur le jeune organisme, en particulier chez les enfants héréditairement prédisposés aux maladies allergiques. Cette sensibilisation serait facilitée par la brièveté et par la grande ampleur de la trompe, au travers de laquelle, aussi bien pendant la déglutition que pendant le vomissement, de petites quantités de lait peuvent arriver dans la caisse.

8) Coté de la M.R. :

droit	gauche	bilat.
35	41	7

9) Structure de la mastoïde :

pnéumatique	compacte	?
22	8	31

10) Suture :	immédiate	éloignée	?	
	15	22	24	
11) Traitement :	incision	révision	op. radicale	médical
	42	11	4	33

Sous la dénomination « médical » sont comprises aussi beaucoup de M. R. spontanément guéries. Il s'agit d'une dizaine de M. R. d'emblée parues au cours d'un rhume, et dont tout symptôme disparu au bout de quelques jours, avant qu'une mesure thérapeutique quelconque eût été réalisée.

12) Causes suspectes de la récédive. (Souvent on rencontre plusieurs causes chez le même sujet.)

Causes:	Anatomiques (cellules)	T. b. c.	Scarlatine	Rougeole	Constitu- tionnelles	Inconnues
N° Récid. .	12	4	9	3	63	25
N° Pat. ...	6	3	4	3	40	20

CAUSES DE RÉCIDIVES

Dans le tableau 12 j'ai groupé les causes suspectes de la récédive. Il s'agit là d'un groupement préliminaire, les causes n'étant pas expressément déclarées dans les journaux cliniques. Elles sortent de l'anamnèse ou du « répert » opératoire.

A) Causes anatomiques.

Tous les auteurs qui ont traité de la M. R. ont énuméré, parmi ses causes, la persistance de cullules mastoïdiennes qui n'ont pas été ouvertes au cours de la première opération. Dans la statistique dont je m'occupe nous avons 6 cas à ce sujet.

Il s'agit de patients qui firent une ou plusieurs M. R. très longtemps après la première Mastoïdite. Pendant de longues périodes, de deux à cinq années, ils sont demeurés en bonne santé, en ce qui concerne les oreilles. À l'occasion d'une angine,

d'une rhinite ils firent une nouvelle otite avec M. R. Pendant la révision on trouva des cellules, tantôt envahies par le pus, tantôt remplies par muqueuse oédémateuse. Quelques-uns d'entre eux firent ensuite une deuxième M. R. tandis que deux patients firent trois M. R., dont une avant, une après une diligente révision. Si ces cellules avaient été infectées dès la première mastoïdectomie, le malade n'aurait pas pu guérir. Nous devons admettre donc qu'elles étaient saines et qu'elles se sont infectées au cours d'une nouvelle infection, dont évidemment elles ne pouvaient pas être la cause.

On ne peut pas dire non plus qu'elles ont, par leur présence, conditionné ou facilité la récurrence. En effet il y a beaucoup de récurrences dans des mastoïdes parfaitement évidées, et il y en a dans des mastoïdes qui contiennent encore quelques groupes cellulaires, sans que ces cellules participent nécessairement au processus inflammatoire.

À l'appui de ce que je viens de dire, je désire citer le cas suivant :

N. G. journal 1071/1934, jeune fille âgée de 10 ans. Elle eut beaucoup d'otites récurrentes ; mastoïdite bilatérale à l'âge de deux ans ; mastoïdite à récurrence gauche, incisée, à 7 ans ; mastoïdite à récurrence gauche à 10 ans, celle-ci aussi incisée. Pendant la convalescence de cette dernière M. R., par suite d'une angine, la cavité opératoire, qui était presque sèche, commença à donner de nouveau. Après une semaine septicémie. Révision. « Autour de l'antre et vers la pointe un réseau de petites cellules à parois médulleuses ». Il s'agissait probablement de cellules néoformées, qui existaient déjà à l'époque de la première récurrence, mais elles ne participèrent pas au processus inflammatoire, de même qu'elles ne participèrent pas à la deuxième récurrence. Ce fut seulement par suite de l'angine qu'elles s'infectèrent.

Si les cellules ont été regardées comme cause de récurrence, cela dépend probablement de la confusion qu'on fait souvent entre vraies et fausses récurrences.

B) Tuberculose.

Ce petit groupe comprend trois jeunes patients qui avaient aussi une affection t. b. c. extrapulmonaire.

J.H.O. Journal 540/1935. Lymphome t. b. c. Mastoïdectomie bilatérale à 8 ans. M. R. droite à 12 ans. Guérison par première.

H.R. Journal 203/1946. Mastoïdectomie gauche à 3 ans. Ensuite beaucoup d'otites à l'occasion de rhumes. M. R. à 6 ans, révision. Encore une M. R. à 20 ans, par suite de rhume. Incision. Eos. sang 6,5 %. À l'occasion de la première M. R. on constata t. b. c. (pas mieux identifiée). Entre les deux M. R. le patient continua à avoir ses otites chaque année, provoques toujours par rhume. Aussi bien la mastoïdectomie, que les M. R. guérissent dans une période normale de temps.

A.G. Journal 1581/1936. T. b. c. abdominale. À 11 mois, précédée de diarrhée, vomissements, rhinite, il fit une mastoïdite droite. Guérison au bout de 3 semaines. Après 5 mois M. R. à l'occasion de rhume. Guérison au bout de 3 semaines, malgré une varicelle qui occasionna un retour de sécrétion dans la plaie.

Dans ces trois cas la t. b. c. n'a joué aucun rôle dans l'apparition des mastoïdites et des M. R., si l'on peut juger par leur allure tout à fait normale. Par contre le deuxième cas était un sujet allergique, tandis que le troisième était probablement allergique.

C) *Groupe scarlatine.*

Ce groupe comprend 9 M. R. chez 4 jeunes patients.

1) *A.N.O.* Journal 869/1938 âgé de 6 ans. Opéré de mastoïdectomie scarlatineuse en mai 1937. Il guérit avec retard. Pendant son séjour à l'hôpital il fut opéré aussi de vég. ad. Douze mois après la guérison il fit une récurrence par suite d'une rhinite. Un abcès dans la cicatrice fut incisé ; l'os était sain. Il guérit dans 12 jours.

2) *N.K.* 7 ans. Journal 374/1938. Il n'avait jamais souffert des oreilles. Le 25/5-1937 otalgie à droite. Il entre en Clinique le 27/5.

Examen otoscopique : A. D. Sur la paroi antérieure du conduit, très superficiellement, un polype gros comme un grain de riz, qu'on aspire. M. T. légèrement rose, bombée. La paracentèse donne issue à un liquide trouble.

A. S. normale. Eos. 3 %.

Les jours suivants la temp. se tient obstinément autour de 40°. Le 3/6 le toit du conduit est baissé. On l'opère le même jour. Système cellulaire irrégulier. Quelques cellules contiennent du pus ; la muqueuse des cellules est partout oedémateuse.

6/6 La temp. est toujours haute. La M. T. gauche est rouge et bombée. P. c.
7/6 Scarlatine. Le malade est transféré à l'hôpital pour maladies infectieuses.
10/6 Mastoïdectomie gauche.

20/8 Guérison.

26/3-1938. M. R. sin. Incision.

5/4-1938 gonflement, rougeur, douleur dans la région mast. droite. Cela disparaît spontanément.

23/4 Guérison bilatérale.

3) H. K. 4 ans. Journal 473/1940.

Cette petite fille fut opérée de mastoïdectomie scarlatineuse bilatérale en 1934. Les cavités opératoires guérirent avec difficulté, mais les deux oreilles continuèrent à couler. Dans le mois de mai 1935 du pus commença à sortir aussi de la cicatrice gauche. On procéda alors à une révision bilatérale et à l'adénotomie et la malade guérit. Après 5 années, pendant lesquelles elle vécut en bonne santé, elle fit soudainement une récurrence droite. L'incision donna issue à beaucoup de pus. Guérison.

4) P. W. 5 ans. Journal 1141/1947.

Mastoïdite scarlatineuse bilat. opérée en mai 1946. M. R. bilat. en octobre. Guérison après traitement conservatif.

De même en mars 1947.

M. R. gauche le 23/6-1947. Eos. 1 %. M. T. légèrement rouge et bombée. Gonflement et rougeur rétroauriculaire. On a fait entrer la petite en Clinique pour prélever du pus, dans le but de préparer l'autovaccin, mais le jour suivant tout symptôme était disparu.

Le 17/8 otite aiguë gauche. Elle fut conduite le même jour à l'ambulatorio, où on constata une modeste otite purulente gauche et rien de pathologique à droite. Deux jours après la petite fit une otite droite. Elle entra en *Clinique après quelques heures*, et on constata gonflement rétroauriculaire, m. t. épaisse, bombée. Cavité nasopharyngienne normale. On pratiqua tout de suite la paracentèse, on donna de la pénicilline et après quelques jours tout symptôme était disparu.

Quels sont les rapports entre l'infection scarlatineuse primitive et les M. R. ?

L'infection scarlatineuse provoque souvent des lésions ostéitiques graves et, peut-être, une diminution de la vitalité tissurale, qui nous fait comprendre la difficulté du procès de réparation ou la chronicisation des lésions. Mais une fois la guérison consolidée, si une récurrence arrive longtemps après, on ne peut pas invoquer la scarlatine pour l'expliquer. La vitalité des tissus, qui paraît diminuée pendant la période de réparation, redevient tout-à-fait normale, à juger de la rapidité avec laquelle ces M. R. sont guéries. Certainement on a énuméré parmi les causes de M. R. la scarlatine. À ce propos j'ai voulu faire une enquête dans l'hôpital pour maladies in-

fectieuses de Lund. Voici le résultat : dans la période 1931—1948 97 patients ont été opérés de mastoïdectomie scarlatineuse, pour un total de 112 opérations. Seulement 4 d'entre eux ont récidivé, pour un total de 9 M. R. Traduit en % cela fait 4 % et 8 %, un pourcentage tout à fait normal.

On peut donc conclure que la scarlatine ne prédispose pas aux M. R.

D) *Groupe Rougeole.*

Il s'agit de deux petites filles de 7 ans, et d'une jeune fille de 17 ans qui ont fait une seule M. R. après respectivement 3 ,2, 10 années. Ces récidives ne présentent rien de particulier dans leur histoire, très brève du reste. La période de temps entre la rougeole et la M. R. est si longue qu'on peut paisiblement exclure un rapport de causalité. Du reste on peut répéter pour la rougeole les mêmes considérations faites à propos de la scarlatine.

E) *Causes inconnues.*

Pour un groupe de 25 M. R. chez 20 patients on ne trouve pas dans les journaux cliniques de renseignements sur les symptômes qui précéderent la M. R. ou l'accompagnèrent pendant la convalescence, et qui soient à même de nous guider dans la recherche de la cause de la récidive. Il s'agit de patients opérés ailleurs la première fois. C'est pour cela que ce groupe se trouve sous la dénomination de M. R. à cause inconnue. Je n'en parlerai donc pas.

F) *Causes constitutionnelles.*

Sous cette dénomination j'ai groupé les patients qui montraient une disposition marquée pour les affections des voies aériennes en général, et de celles supérieures en particulier ; des oreilles ; souvent de la peau ; quelquefois du tube digestif. Ces affections figurent en relation immédiate avec le début d'une M. R. ou l'accompagnent pendant la convalescence.

C'est le groupe le plus nombreux : 40 patients avec un total de 64 M. R. (= resp. 65 % et 70 %).

Manifestations pathologiques	Rhinites	Rhinites, angine, bronchite, sinusite, Otites, Eczéma, Urticaire, Sulfa-exanthéma Vomissement-diarrhée	Otites
N° Patients	6	28	6
N° M. R.	8	40	15

Dans ce groupe figurent 7 patients pour un total de 15 M. R., qui ont été examinés du point de vue allergique dans les années 1946—47—48 par le Dr. Koch, qui s'occupait alors des otites chroniques allergiques. La diagnose de nature allergique repose sur l'éosinophilie du sang ou de la sécrétion ou de tous les deux, sur les résultats du test, sur l'influence favorable d'une diète d'élimination, sur l'effet de la thérapie désensibilisante spécifique ou aspécifique. Pour l'éosinophilie nous avons des valeurs qui arrivent quelquefois à 20—22 % dans la sécrétion auriculaire, tandis que pour le sang le maximum est de 14 %. Ces valeurs ont toutefois de sensibles oscillations dans les diverses périodes de la maladie chez le même patient. Trois types d'allergie y sont représentés : allergie bactérielle, allergie pour substances inhalantes, allergie alimentaire. L'anamnèse et l'évolution clinique ont été particulièrement soignées. Il s'agit de sujets qui font souvent des rhinites, des angines, des otites. Les végétations adénoïdes ou les tonsilles n'étaient pas en cause. Plusieurs d'entre eux ont eu des manifestations allergiques, telles que eczéma, urticaire, désordres digestifs.

Je vais donner, en résumé, quelques histoires cliniques.

P. S. (journal 623/1946) jeune homme de 19 ans.

En 1936, âgé de 9 ans, il fut opéré de mastoïdectomie radicale droite et de sinusite maxillaire droite. En 1944 il fit une otite aiguë gauche, compliquée de mastoïdite. L'examen culturel donna streptococcus. Eosinophilie : secr. 22 % sang 2 — 14 — 6 %. Le test donna des réponses très faibles. Désensibilisation ad modum Freeman. Il guérit après deux mois, mais il fit une récurrence après deux années : otitis media allergica bilat. + mastoïditis récid. sin. Incision. Examen bactériel : difteroides + proteus vulgaris. Eos. 4 %. Désensibilisation avec Stafital. Guérison en 17 jours.

A. I. Journal 1334/1947. Âgé de 3 ans.

Il fit en 1946 une ethmoïdite aiguë gauche, plusieurs otites, une M. R. droite. En 1947 encore des otites et 3 M. R. Aussi bien les otites que les M. R. furent

occasionnées toujours par des rhumes. L'éosinophilie était 5,5 %, 2 %, 9 %, 2 %. L'examen culturel donna streptococcus, staphylococcus aureus, pseudomonas pyocyaneus. Une seule fois l'incision rétroauriculaire fut nécessaire. L'otite et l'œdème rétroauriculaire se manifestaient subitement (phénomène contrôlé en clinique). Le test fut négatif pour alimenta et pour inhalantia. Un autovaccin fut apprêté avec le staphylococcus aureus. Une injection intradermique de 0.05 de ce vaccin donna une « delayed reaction » après 24 h. (10×10 mm). Une dose plus forte donna une réaction de 15×20 mm. Aucune réaction, au contraire, chez trois enfants contrôle. Il s'agissait donc d'une allergie bactérielle. On procéda à la désensibilisation, et à la dixième journée le malade était guéri. Trois mois plus tard nouvelle M.R. occasionnée par rhume. Cette fois l'eos. était 0 %, l'examen culturel donna pseudomonas. Sécrétion auriculaire : N. ++++ Eos. rares.

Dans ce même groupe figurent 13 patients pour un total de 25 M. R. Ils montrent les mêmes symptômes que j'ai remarqué chez les patients allergiques : rhinites fréquentes, angines, beaucoup d'otites ; quelquefois eczéma, bronchite, sulfaexanthème, et tout cela en coïncidence avec une M. R. Puisque les recherches allergiques chez ces patients n'ont pas été faites, ou bien sont incomplètes, je les regarde comme « probablement allergiques ». Voici quelques histoires cliniques :

S. A. I. (Journal 1344/1932) enfant âgé de deux ans.

Il a une histoire de rhinopharyngites, otites, pertussis, bronchopneumonie. Il fut opéré de mastoïdectomie bilatérale à l'âge de 8 mois. L'examen bactériel de la sécrétion auriculaire fut positif pour le b. de Löffler. Il fit deux M. R. À l'occasion de la première M. R. il fit un eczéma aigu sur la région sousaillaire gauche et sur le tronc. À l'occasion de la deuxième M. R. je trouve dans son journal cette annotation : « Pendant le long séjour en Clinique ses oreilles ont, tantôt plus, tantôt moins, toujours coulé. Sécrétion muqueuse ou mucopurulente, inodore. Quand la sécrétion augmentait on pouvait observer des éruptions papuleuses sur le visage et sur les bras. État général bon. Membranes tympaniques pâles, épaisses, avec de larges perforations centrales. Muqueuse promontoriale légèrement rose. Ouïe bonne ».

Un deuxième cas, P. W. journal 1141/1947, regarde une fillette âgée de 5 ans, opéré de mastoïdectomie scarlatineuse bilatérales en octobre 1946 et en mars 1947, une M. R. gauche en juin et une M. R. droite en septembre 1947. Ce qui caractérisait ces récidives était la rapidité avec laquelle elles surgissaient et disparaissaient, sans suppuration, presque sans fièvre, avec une réaction de précipitation entre 10—22. La durée de ces récidives a été d'un minimum de

N:o Progressif	Journal	Année	Age	N:o M. R.	Rhinite	Angine	Oùte	Bronchite	Eczéma	Urticaire	Vomissement	Diarrhée	Oedème dans les cellules	Bactères	Eosinophilie sans / secrét	Test allerg.	Sulfa	Pénicilline	Désensibil.
1	223/46		19	1	Sinusite maxill.		+++							strepto, diffe-roides, proteus vulg.	4 0/0 2 14 0/0 22	+			+
2	203/46		20	3	+++	+	++								6,5 0/0 0		+++	+	
3	955/46		9	3		++							++			+++	+		
4	85/47		4	1	+++		+++								4 0/0 5 0/0 3 1 0/0	+++	+		
5	891/47		8	1	+		+++							pseudo-monas pyocyaneus			+	+	
6	1334/47		5	4	+++		+++							stafyloc. albus strepto. pyocyan.	9 5,5 0/0 2	++	+	+	+
7	411/48		11	2	++		+++							Stafylo-aureus.	2 0/0 +	+			

M. R. allergiques.

3 jours à un maximum d'une semaine. Une seule fois on pratiqua une paracentèse, qui donna issue à mucopus en modeste quantité. La rougeur de la membrane tympanique et l'oedème rétroauriculaire disparaissaient en dehors de toute thérapie. Une seule fois, quand fut pratiquée la paracentèse, on donna de la pénicilline. Pas de adénoïdes. Eos 1 %.

On peut dire avec Mouret que « souvent l'inflammation aiguë de la caisse et des cavités aériennes n'est qu'un simple rhume des cavités de l'oreille moyenne, qui guérit facilement sans trépanation ». Ce rhume se traduit anatomiquement par un oedème des tissus muqueux et des tissus cicatriciels ; la rapidité avec laquelle cet oedème se produit et disparaît a une très grande analogie avec les oedèmes transitoires de Kennedy et avec l'oedème angionéurotique de Quinke, qui reposent sur une base allergique. J'ai voulu, par brièveté, me borner à deux exemples, mais j'espère avoir donné une idée du criterium suivi pour la diagnose de M. R. de nature probablement allergique.

Nous avons, enfin, dans le même groupe, 19 patients pour un total de 23 M. R. dont les symptômes ne sont pas si prononcés pour nous autoriser à les soupçonner d'allergie.

En conclusion on peut dire que sur un total de 90 M. R. 15 sont de nature assurément allergique (17 %) ; 25 sont de nature probablement allergique (28 %) tandis que pour 50 on n'a pas de données suffisantes pour pouvoir juger de leur nature.

L'otite m. allergique est désormais une entité clinique indiscutable. À sa connaissance ont contribué, parmi les autres, Lewis, Smirnov, Proetz, Dohlman, Koch. L'existence d'une allergie mastoïdienne, tout en étant une conséquence naturelle, ou, si l'on préfère, un aspect de l'allergie auriculaire, n'était pas connue jusqu'ici. J'espère qu'une telle connaissance apportera une contribution, si modeste soit elle, à la question des M. R. Il est souhaitable qu'à l'avenir toute M. R. soit examinée du point de vue allergique. De même, comme mesure préventive, toute mastoïdite primaire chez les jeunes et les enfants,

N:o Progressif	Journal	Année	Age	N:o M. R.	Rhinite	Angine	Otite	Bronchite	Eczéma	Urticaire	Vomissement	Diarrhée	Oedème dans les cellules	Bactéries	Éosino-philie	Test	Sulfa	Pénicilline	Désensibil.
1	1344/32		2 1/2	2	++	+	++		+	+				Löffler					
2	1006/32		15	1	++		++							pyocyaneus					
3	454/38		12	3	++	+	++							pyocyaneus					
4	1581/35		17 m.	1	++	+	++			+									
5	1324/36		20	1	++	++		+			+		+		2 0/0				
6	1325/37		7	2	++	+				++			+		3 0/0				
7	656/47		19	2	++		++		+				+						
8	942/38		6	1	++		++						+		3 0/0				
9	368/41		59	3	+		++			+			++	Staphilococcus Strepto-hemol.			+		
10	609/44		16	1	++		++										+		
11	415/47		6	1	++		++								3,5 0/0		+		
12	1141/47		6	6			++						+				+		
13	1405/47		10	1	++		++							Streptococcus	3 0/0		+		

M. R. Probablement allergiques.

SUMMARY

The author has studied the Recurring Mastoiditis, which have been treated at the E. N. T. Clinic of Lund during the period 1931-1948, in order to investigate if an allergic constitution might be one of the causes for relapse. He separated the "false" R. M. from the "real" ones. Only the latter have been object for his examinations.

On a total of 1765 mast-ect. there is 90 R. M. (= 5.1 %) by 61 patients. During the last three years it has been shown that the total number of mast-ect. has deminished (resp. 88, 97, 15) at the same time as the percentage of R. M. has increased (resp. 12.5—15.5—26 %). All measures, which have been taken to prevent relapses, (complet evacuation of the air-cell system, adeno-ectomy, tonsillectomie etc.) have been insufficient. Presence of cells left over at the first operation does not influence the frequency of relapses. The same may be said about scarlatina and measles.

On the other hand the allergic constitution plays an important rôle: 17 % of the R. M. have proved to occur in allergic patients; 28 % by probably allergic patients.

Concerning the age, 62 % of the R. M. have been in the age-group 1-10 years, 20 % between 11-20 years, 18 % between 21-75 years.

In order to prevent the R. M. one must also take into account the possible allergic constitution of the patients.

ZUSAMMENFASSUNG

Um auszuforschen, ob eine allergische Konstitution eine von den Ursachen des Rezidivs sein könnte, hat der Verf. die R. M. studiert, die in den Jahren 1931—1948 in der Ohrenklinik zu Lund behandelt worden sind. Er sonderte die falschen R. M. von den echten ab. Nur diese sind Gegenstand seiner Untersuchungen gewesen. In einer Gesamtzahl von 1765 Mast-ect. sind 90 R. M. (= 5,1 %) auf 61 Patienten. Während der drei letzten Jahre hat die totale Zahl der Mast-

ect. abgenommen (88, 97, 15 resp.), während die Prozentzahl der R. M. zugenommen hat (12,5 — 15,5 — 26 % resp.). Alle Massnahmen, die ergriffen worden sind, um die Rezidive zu verhindern (vollständige Ausräumung des Zellsystems, Adenoidectomie, Tonsillectomie, usw.) haben sich als unzureichend gezeigt. Die Anwesenheit der von der ersten Operation zurqckgebliebenen Zellen beeinflusst nicht die Frequenz der Rezidive. Dasselbe kann von Scharlach und Mazern behauptet werden.

Auf der anderen Seite spielt die allergische Konstitution eine bedeutende Rolle: es hat sich gezeigt, dass 17 % von den R.M. bei allergischen Patienten auftreten und 28 % bei wahrscheinlich allergischen Patienten.

Betreffs des Alters gehören 62 % von den R. M. zu der Altersgruppe 1—10 Jahren, 20 % 11—20, 18 % 21—75.

Um die R. M. zu verhindern, muss man auch die etwaige allergische Konstitution der Patienten im Auge halten.

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LETTERS RECEIVED

(Submitted by doctor Roman Alemany-Vall, Barcelona)

Coryza. Causes et traitement par le Dr. Roman Alemany-Vall paru dans « *Anales de Medicina* » juin 1946. Barcelona.

L'auteur parle du rhume commun, décrit sa symptomatologie et établit la différence avec les coryzas allergiques ou franchement infectieux. Il parle de la sinusite hyperplastique comme cause de coryzas, ainsi que du coryza par sinusite séro-purulente. Il parle des déviations et crête de la cloison qui n'ont pas une grande valeur comme cause de rhinite spasmodique.

Les refroidissements comme cause de la diminution de calcium ou d'hémoglobine, ou des réactions vaso-motrices de la peau. L'influence de la réserve alcaline dans certains coryzas est importante, et l'auteur donne de l'aspirine ou du bicarbonate selon qu'il y a de l'alcalose ou de l'acidose dans les urines.

Il parle de certaines habitations (chambre à coucher) comme cause de coryzas ; il recommande de ne pas donner de vaso-constricteurs locaux et d'éviter les antiseptiques nasaux forts qui font plus de mal que de bien.

Summary of rhinitis and asthma caused by pollen by Dr. R. Alemany-Vall, Barcelona. *Anales de Medicina*. Oct. 1947.

The author refers to various influences in the patient's surroundings which favour the development of an attack. The finding of the plant the pollen of which is responsible for the symptoms is very important to rendering the treatment specific. He speaks of the different quantities of pollen of gramineous plants of which he has found and examined ninety-seven species within the municipal boundaries of Barcelona from March to July; he finds that the pollen of *Parietaria officinalis* is a frequent cause of simple and complicated rhinitis followed by asthma; he has observed several cases of this kind among people living in the country and suburbs of larger cities. He studies hay fever in which he often observes that the nasal mucous membrane is red and irregularly swollen even in old and stationary cases.

Summary of allergic reactions and lesions of the skin by Dr. R. Alemany-Vall, Med. Clin. Dec. 1947, Barcelona.

The author speaks of simple and quite well-known dermographism as a pre-stage to a true sensitization; also of the demographism appearing together

with macules after gastrointestinal disturbances. He refers to the specific skin reaction to the antigen and the dermal hypersensitivity shown to numerous substances which, however, are not really considered as true causes of the condition. He speaks of various skin reactions in the form of pruritus, papules, urticaria and angioneurotic edema in patients with food sensitiveness confirmed by previous gastrointestinal disturbances and previous positive scratch test. The author also refers to skin lesions appearing as slight local eczemas, generally on the face, the neck and the hands which respond to an alimentary regimen and with positive scratch test to food. Slightly toxic dermites and a case of hypersensitivity to *Primula auricula* are also mentioned.

Etiopathogénie des lésions cutanées allergiques par le Dr. Roman Alemany-Vall paru dans « *Anales de Medicina* » Marzo 1948, Barcelona.

L'auteur parle des lésions cutanées qui persistent malgré les traitements locaux, mais que l'on peut faire disparaître en suivant un traitement antiallergique de suppressions des antigènes par un régime alimentaire exclusif, ou plus simplement par un traitement antiallergique général qui fait disparaître les lésions en un temps relativement court de 1 à 4 semaines, malgré qu'elles existaient depuis des mois et quelques fois des années. Ce sont des lésions simplement érythémateuses ou papuleuses et de démangeaisons, de vésicules peu nombreuses et avec tendance à la liquéfaction ; en général il n'y a aucune infection visible, bien qu'il y ait d'autres lésions associées ou occasionnées par le grattage.

L'auteur parle de lésions cutanées par contact, de lésions professionnelles, etc. etc. de lésions cutanées par pollen et champignons.

Non seulement les oeufs, le lait, le poisson, mais également la laitue, les épinards etc. peuvent occasionner de brusques troubles gastro-intestinaux, et quelques heures après des éruptions cutanées variées et très étendues.

About alimentary origin of some eczemas of hands by Dr. R. Alemany-Vall ("Le Monde Médical" no. 924, 1948), Barcelona.

This subject has been referred to in other articles which appeared two years ago; since then, the articles of Flood & Perry and Rowe have been published.

The lesions are erytemas, papules and vesicles on the hands and fingers in all cases; in the more serious cases there are also similar lesions in the skin of the abdomen, arms etc.; sometimes there are very extensive angioneurotic edemas of some days' duration (face and hands); it is necessary to examine extracts of food in the skin, but they may be negative or only slightly positive.

Elimination-diets may be valuable to find the food which causes the affection of the skin; they require much time, and the patients must be under

careful observation, but if the work is successful, desensitization is not necessary.

Ten cases with long clinical histories are recorded.

Treatment of asthmatic attacks by Dr. R. Alemany-Vall, Barcelona Med. Clin.

Junio 1948.

Although the author does not share the orthodox point of view of tuberculous asthma, he believes in the existence of a tuberculinic asthma which responds promptly and satisfactorily to tuberculin; the patients are young persons with initial attacks, for a few years, limited to more or less persistent wheezing râles interrupted by slight and medium dyspneic attacks; globular sedimentation is normal.

The author also refers to the high glycemia in asthmatic patients not fully responsive to the application of bacterial vaccine which causes in some cases only a slight, generally persistent, bronchitis; in other cases the glycemia will be accompanied by a slight glycosuria without diabetic symptoms. Good and lasting results are obtained in both groups with regimen and insulin administered in small doses. We do not refer here to those high doses of insulin that provoke a collapse.

In asthmatic conditions euphilin, bloodletting etc. are resorted to. The author mentions various conditions, in tuberculous patients, of a more or less asthmatoïd character and the behaviour of tuberculin in these cases; also cases of infectious asthma with high and persistent temperature and asthma disappearing with the fever; he also speaks of nasal asthma and asthmatic bronchitis, administering penicillin in aerosol.

Cas d'asthme bronchial suivi d'autopsie — par les Drs. Ferrer Solervicens R. Alemany-Vall, et Gonzalez-Ribas. — Publiée dans le no. 286 de « Los Progresos de la Clinica ». Madrid.

Les auteurs décrivent un cas d'asthme chez une femme de 50 ans qui après une extraordinaire amélioration à la suite de divers traitements, fait une rechute au bout de deux mois et après son entrée à l'hôpital, meurt en pleine attaque asthmatique ainsi que le démontre son autopsie.

L'autopsie démontre les poumons dilatés, les grandes bronches pleines de mucosités très consistantes, et les petites bronches de parois peu résistantes pleines de filaments mucopurulents très longs.

Sur les microphotographies on voit la muqueuse des grandes bronches hyperplasiée et descamée. La submuqueuse est très infiltrée d'éosinophiles, et montre une forte hypertrophie de la couche musculaire. Un tampon muqueux obture presque les bronches.

Les auteurs décrivent ensuite plusieurs cas de mort par asthme bronchial avec autopsie, et 45 cas trouvés dans la littérature mondiale.

Summary of a few cases of asthma and rhinitis caused by flour by Dr. R. Alemany-Vall. *Medicamenta* — 15-IV-48, Madrid.

The author refers to cases of rhinitis and asthma due to sensitization to flour—which are different from respiratory affections by mechanical action. He establishes the existence of slight allergic dermites in the zones of flexion of the limbs, by hematogenous action, which disappears in a month or six weeks after changes in the patient's surroundings. He attributes a certain value to the reappearance of local eosinophilia, whether nasal or in the sputum, as a prelude to a more or less near resumption of attacks whenever the patient returns to a flour-containing atmosphere.

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